The Influence of Psychotherapy and Depression on Platelet Imipramine and Paroxetine Binding

Thesis

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THE INFLUENCE OF PSYCHOTHERAPY AND DEPRESSION ON PLATELET IMIPRAMINE AND PAROXETINE BINDING

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ABSTRACT

[^{3}H]-Paroxetine and [^{3}H]-imipramine are known to label with high affinity, a site which is associated with the serotonergic transporter in brain and platelets. [^{3}H]-imipramine binding to platelet membranes appears to be a biological marker in depression, the B_{max} of platelet imipramine binding being significantly decreased in untreated depressed patients by comparison with healthy volunteers.

Psychotherapy is claimed to produce significant improvement in depressed subjects without the use of drugs. This study aimed to determine whether differences were apparent in binding values for [^{3}H]-paroxetine and [^{3}H]-imipramine binding in subjects suffering from mild depression compared to controls, and how these values changed as the subjects went through a period of psychotherapy. In addition, psychiatric state was assessed using the BDI, the MAACL and the GHQ-28. Binding levels were then correlated with the scores obtained from the self-administered questionnaires to determine the relationship between binding and psychological state. Similar data were also collected from a group of nurses, who it was predicted would be suffering from a higher level of depression than the general population and would remain untreated.

The results from the psychotherapy group indicated that clients entering the study were significantly more depressed than controls (BDI $P<0.05$; MAACL $P<0.01$ GHQ-28 (excluding somatic symptoms) $P<0.05$) and had lower imipramine binding. Furthermore as they went through the period of psychotherapy their psychological test scores fell, and imipramine binding levels rose, to a level equivalent to the control values. Levels of [^{3}H]-paroxetine binding to platelets did not appear to be affected by psychological state, at least in these patients.

In the group of nurses, both binding measurements were significantly lower than controls at most time points throughout the study ($P<0.05$) indicating lower affect. However psychological questionnaires indicated less distress in the nurses group than the control

group (particularly BDI and GHQ-28). This is discussed in terms of possible coping strategies employed by nurses.

It was not possible to correlate the questionnaire scores with the results from the binding assays for clients, controls or nurses. There was no significant evidence of sex differences, either in binding parameters or questionnaire scores, and no evidence of seasonality of the binding levels. Proposals for future work are suggested.

CHAPTER 1

INTRODUCTION

Within the many approaches to the explanation and treatment of psychic disorders, it is possible to distinguish two broad traditions, often seen in the past, not merely as alternative but in actual contradiction with each other. Although the two schools of thought are now recognising the values and usefulness of each other to a greater extent, differences and prejudices still exist. To simplify, the two views may be presented as follows. On the one hand, biological psychiatry is committed to the view that much if not all psychiatric illness is the consequence of disordered molecular mechanisms within the brain, and that the appropriate treatment is therefore by means of drugs which interact with neurochemical systems in such a way as to rectify or alleviate molecular imbalances or deficits. On the other hand, the psychotherapeutic tradition seeks to explain psychic distress in terms of precipitating events in an individual's past life, whether in the distant past of early infancy or childhood trauma, or in the crises of present circumstances and way of living. Therapy then involves revealing and coming to terms with past personal history and learning to live with or transcend present difficulties. Protagonists of each of the two distinct traditions have frequently been sceptical or even hostile to the claims of the other.

Biological psychiatry has been critical of psychotherapy as not conforming to the norms of science to which biomedicine aspires, as being expensive for the patient and dubious in outcome. There has been a vigorous polemic in the literature about the significance and interpretation of the various outcome studies in psychotherapy which have been undertaken in the past two decades, over, for instance, whether psychotherapy is more effective than "placebo" treatment - or what constitutes a placebo in the context of the particular relationship of therapist to client. Additionally, if psychotherapy *is* effective, is any one of its many varieties more effective than any other? (e.g. Smith *et al.* 1980; Prioleau *et al.* 1983; De Witt *et al*. 1983; Aveline 1984; Shepherd 1984; Holden 1986).

On the other hand, psychotherapy has criticised biological psychiatry for its reductionist

philosophy, in which existential distress is perceived as epiphenomenal to mere molecular happenings, and has charged it with mistaking symptoms for causes, and ignoring the whole person in his or her psychic and social context in favour of the administration of drugs which may mask rather than treat a condition - or may even have iatrogenic consequences. Again, there is an extensive literature.(e.g. Sedgwick 1982; Hill 1983)

It was the aim of this project to explore the possibility of approaches which might help to bridge the gap between these two broad therapeutic traditions. I begin from the position that any scientific theory of human behaviour, intentions and actions must assume that brain processes on the one hand, and human experiential states (to put it at its most general) on the other, must be related. It therefore follows that there are biological (or more specifically biochemical) ways in which the brain state of, for example, a depressed person differs from that of the same person when "normal" - that is, when not depressed - or from the average brain state of a population of undepressed and unanxious people. Hence, in so far as psychotherapy modifies a person's experiential state, it must also modify their biology and brain state (Rose 1984). In so far as biological psychiatry and psychotherapy have similar outcomes in improving a psychically distressed person's condition, their effects on that person's biology and brain state are likely to be similar.

Two things follow. If the claims of biological psychiatry are valid, there should be biochemical markers for conditions diagnosed as depression, anxiety and the affective disorders in general. If the claims of psychotherapy are valid, then psychotherapeutic treatment of persons suffering from one of the affective disorders should not merely improve their psychic state but should result in changes in the biochemical marker(s) for the condition. If such a change, in a marker accepted by biological psychiatry, could be shown to occur as a consequence of psychotherapeutic treatment, it would be of considerable theoretical and social interest in helping to bridge the gap between "biological" and "psychic" modes of accounting for psychic distress, and also between biological psychiatry and psychotherapy as modes of treatment for that distress. The outcome of this research could therefore be of help in developing and improving rational treatment approaches. Furthermore it was hoped that the data would provide longitudinal evidence of biochemical

changes in brain state correlated with psychological changes.

It was not the intention of this research to try and determine whether or not psychotherapy was an effective treatment for depression or not, and no placebo control group was employed. The definition of placebo as proposed by Shapiro (1964) is as follows "any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect on a patient, symptom syndrome or disease, but is objectively without *specific* activity for the condition being treated". It would have been extremely difficult to provide a useful placebo group for this study for the following reasons. Firstly it is very difficult to control for psychotherapy using a placebo pill, not least because the patient will know which treatment they are receiving, and the ethical issues of using placebo outside a rigorous clinical setting are enormous. It is often said that placebo deceives the patient, although providing adequate explanation of the study is given, this should not be the case.

Secondly I was only intending to use a very mildly depressed group and knew the sample size would be relatively small. Placebo response rates in drug trials of antidepressants are very high (around 30-50%) and are greatest in patients with less chronic depression (Khan *et al* 1991). This is due to; the placebo effect per se, the warmth and encouragement of medical staff, the assignment of the 'sick role' (which helps relationships with family, friends and employers), the faith that both the patient and the physician has in the medication and extensive analysis as part of the diagnostic procedure. There is also evidence of a 'dose response' in placebo trials, where the more tablets the patient is given the more they improve. Given the small sample size it was not likely to detect a difference between effective treatment (around 60-70% with anti-depressants, (Brown 1988)) and placebo. Therefore the control sample was chosen as a 'normal' group in whom no change was predicted.

The third major problem with using a placebo control is the risk of suicide. Suicidal ideation is widely recognised as a common symptom of depression (Blumenthal 1988, Montgomery *et al* 1988; Adam 1985) and is not directly related to the severity of the

depression - in fact a very common time for patients to commit suicide is as they start to recover. Various studies have estimated that between 50 to 90% of people who commit suicide are suffering from depression and 35-79% of suicide attempters (Review Adam 1985). The variation in these data is probably largely due to the inaccuracy of retrospective analysis.

Several studies in the past have used waiting list patients as controls and in this way attempted to compensate for spontaneous remission of the disease. However in this study it would have meant clients waiting for one year before receiving any help, and this is obviously unethical. Other researchers have used inexperienced therapists working with patients to act as controls, however given the complex and delicate nature of the therapist/patient interaction this approach is potentially very dangerous.

The group of control subjects used in this study were taken from the Open University and were intended to act as a population 'norm'. It was assumed that they would not be suffering from any depressive disorder or any significant level of stress. To expand the scope of the study it was decided to add a group of nurses, who are known to suffer from a higher level of stress and depression than any other members of the health profession (Wolfgang 1988a) although stress levels tend to be high in all health professionals (e.g. McCue 1986).

Stress is not necessarily negative, it is a natural adaptive response to job and organisational demands, constraints or opportunities. But when it becomes too severe it can seriously impair the performance of the employee in the work environment and eventually at home. The general work stress health model (e.g. House 1981; Katz and Kahn 1978) postulates that objective work conditions can lead to perceptions of stress. Perceived stress in turn leads to boredom, dissatisfaction and turnover, and to individual strains such as anxiety, depression and physical illness. Additionally the stress health model hypothesises that internal characteristics (i.e.personal characteristics) and external characteristics (i.e. the situation) will have both direct and interactive or moderating effects. A relatively consistent link has been established between perceived role stress, satisfaction and psychological

well-being. However attempts to confirm the moderating effects of factors such as social support have had only limited success (Bheer and Bhagat 1985; Cohen and Wills 1985). Sutton and Kahn (1986) proposed that understanding of events, prediction of events and control of events would reduce perceived stress and increase satisfaction and well-being. The hypothesis was tested by Tetrick and LaRocco (1987) and whilst some improvements were made in levels of perceived stress and satisfaction, there was no change in psychological well-being.

The sources of stress in nursing can broadly be considered as threefold. Firstly there are the fundamental conflicts; such as being responsible for other peoples lives. Secondly there is the issue of stereotypes; idealised stereotypes conflict with unpleasant work and failing to cure the patient. Thirdly there is social relevance; nurses are isolated to control the issues they symbolise - through professionalism and social isolation (Marshall 1986). More specifically the identified stressors are; the death of patients, uncertainty about patient treatment, inability to meet patient needs and expectations, looking after dying babies, facing staff shortages, communication and interpersonal problems with medical staff and supervisors, family and life crises, poor self esteem, insecurity about ones knowledge and competence and fear of failure (Anderson and Basteyns 1981; Bailey *et al* 1980; Barstow 1980; Boxall and Garcia 1983; Cronin-Stubbs and Velsor-Friedrich 1981; Dewe 1987: Fountain 1984; Gray-Toft and Andersson 1981; Ivancevich and Matteson 1980; Marcus and Popovic 1985; Parkes 1985).

Whether or not different types of nursing are more stressed than others is a well researched area from which it is very difficult to draw any conclusions. Parkes (1980;1982) found that generally medical wards were more stressful than surgical whereas Ivancevich *et al* (1982) found no significant difference. In another study Cavagnaro (1983) compared stress factors of critical care nurses with other units and found they were significantly more stressed than anesthetic nurses. However Keanne *et al* (1985) did not find any significant difference in burnout reported by intensive care unit (ICU) versus non-ICU nurses, and Chiriboga and Bailey(1986) also found no difference in burnout rate between critical care and non-critical care nurses. Studies comparing nurses from cancer units with other units have found

significantly more mood swings, relational problems and difficulties in discussing the patients condition than other units (Gray-Toft and Anderson 1986). A study of psychiatric nurses (De Leo *et al* 1982) found that psychiatric nurses were more likely to suffer from depression and to a lesser extent anxiety than general nurses. Overall it is not clear whether any one type of nursing is more stressful than others, what appears to be more important is the working environment (Chiriboga and Bailey 1986). Motowidlo *et al* (1986) in a pair of large studies involving nearly 400 nurses identified interpersonal aspects of job performance (e.g. sensitivity, warmth, tolerance) and cognitive/motivational aspects (e.g. concentration, composure, perseverance and adaptability) as the factors which most significantly correlated with self-reported perceptions of stressful events, subjective stress depression and hostility. They identified 45 stressful events for nurses and hypothesised that the frequency and subjective intensity of these events leads to depression which in turn causes a deterioration of interpersonal and cognitive/motivational aspects of job performance. Age appears to be a very important factor in the amount of stress experienced by nurses (e.g. Livingstone and Livingstone 1984) the younger the nurse, the more likely they are to suffer from stress. Numerof and Abrams (1984) have argued that the citing of factors such as feelings of insecurity, to account for nursing stress rests largely on anecdotal evidence. They list age, role status, time since graduation, job tenure, area of nursing and interpersonal needs as the most important factors in job stress. The majority of work on nurses has focused generally on stress rather than looking directly at depression, however it is well established that stress and depression are closely associated.

GENERAL HYPOTHESES

In view of the the general concepts discussed above, the hypotheses for this research were:-

a) Clients in psychotherapy and nurses would be more depressed than controls at the start of the study, and this would be detectable both by psychological questionnaires and by one or more biochemical marker(s).

b) That as the study progresses the scores from the psychological questionnaires and the biochemical marker(s) will improve for the clients such that their values approach similar

levels to the controls.

c) That the nurses scores on psychological questionnaires and biochemical markers will not improve over the time course of the study.

CHAPTER 2

DEPRESSION: THE DISORDER AND OPTIONS FOR TREATMENT

How is depression defined?

Everyone has at some time in their lives felt "depressed", this is a normal experience in times of adversity. It is largely for this reason that clinical depression is so hard to define and so often misunderstood. The term depression may refer to an ephemeral mood, a sustained affective change, a symptom, a syndrome or a psychiatric illness. Depression as a result of adverse circumstances or bereavement is considered "normal", but when it becomes inappropriate in severity, persistence or precipitating circumstances it is considered "abnormal" and requiring treatment. It is important to remember that it is largely not the individual, but society, which dictates the limits for "normality". This is exemplified rather neatly by a quote from the seventeenth century playwright Nathaniel Lee "They called me mad" he protested "and I called them mad and damn them they outvoted me" (Potter 1991). Although depression can be secondary to a number of factors (physical illness,other psychiatric illness or drug therapy) it is most commonly the primary condition characterised by a wide range of symptoms. Depression is heterogeneous with regard to biology, treatment response and prognosis. Therefore depression probably consists of a number of pathophysiologically distinct conditions which we arbitrarily classify as one. This is illustrated by the variety of descriptions of depression given by depressed people. Nairne and Smith (1984) quote a number of patients, examples of which are given below.

"For me, to be depressed means a cold empty feeling that I haven't been nice enough to be happy" Janice

"Depression feels like I can't handle anything anymore. It feels like things are not in my control" Theresa

"I feel as though I'm at a fancy dress party wearing a sack. Nobody can guess who is inside it and I cannot explain who I am" Penny

"Depression overcomes your whole being. You seem to be enveloped by feeling low. It

erodes your confidence and your motivation. You want to withdraw into a world of your own and opt out of the ordinary world". Patricia

Depression is broadly subdivided in terms of causality and symptomatology as shown in the quotes below taken from the Penguin dictionary of psychology (Reber 1985):

Endogenous depression "Depression resulting from "internal" factors. The term is used clinically when there is no apparent precipitant. (Many clinicians now prefer not to use this term believing that there will always be a precipitating event.)

Exogenous / Reactive depression Depression resulting from events occurring in one's life.

Neurotic depression "Ordinary" severe depression (used to cover any depression that is not psychotic)

Psychotic depression Severe depression in which the individual loses contact with reality and suffers from an array of impairments of normal functioning.

Unipolar depression The qualifier unipolar is used for cases in which the depressive episodes recur without the appearance of the manic phase that is observed in the classic form of **Bipolar disorder.**

With the exception of unipolar versus bipolar the above definitions are losing popularity (Opjordsmoen 1991). Unipolar and bipolar depression are more clearly different in their symptomatology and although they have been argued to be clinically and genetically homogeneous, different treatments are often used for the two disorders (e.g. Lithium has tended to be used for bipolar disorder - although it is also used in unipolar disorder).

A Sociological view of depression

Although depression is an illness common to all classes of society, it occurs with highest frequency amongst poorer working class females. Brown and Harris in 1978 studied the incidence of neuroses (using the Present State Examination PSE) in the Camberwell area (a mainly working class area of inner London) and found that about one quarter of working

class women with children were suffering from some form of neurosis - mainly severe depression. The incidence amongst a similar group of middle class women was only 6 percent. A large proportion of these depressed individuals had suffered severe threatening events in their lives within the last year, such as loss of husband or income. The use of drugs, and in particular tranquilisers was very high.

Brown (1977) argues that depression is a social phenomenon. In comparison to the women studied in inner London depression is almost absent from women with children living in the Outer Hebrides irrespective of social class. Brown argues that biological or genetic factors are unlikely to have a primary role in the aetiology of the disease, but does not argue that they are not implicated. He believes that depression is precipitated by certain kinds of severe life events and difficulties and found that this correlated well with women suffering from depression whether or not they had been previously diagnosed or were picked up by the investigation. However the provoking agents themselves are not sufficient to bring about the disease, although they do determine when the disorder occurs. This was illustrated in the studies mentioned earlier, in that a severe life event and or difficulty is more likely to precipitate depression in a working class mother in inner London than a middle class mother in inner London, who is more likely to develop depression than a woman of either class living in the Outer Hebrides.

In addition there are a set of vulnerability factors which make a precipitating event more likely to result in a bout of depression. These are the lack of a close relationship with a husband or boyfriend, three or more children under fifteen at home, unemployment and loss of the mother before the age of eleven. Loss of other relatives during childhood or parental separation can also influence the type and severity of the depressive episode. Brown (1977) termed these 'symptom formation factors', loss by death is strongly associated with psychotic-like depressive symptoms whereas other losses such as parents separating is more likely to lead to neurotic-like depressive symptoms. Two crucial facts emerge from this model: firstly, provoking life events involve major losses, or sometimes major difficulties or threat of loss; secondly, if no vulnerability factors are present then provoking agents rarely bring about depression. Oatley (1984) described depression as

occurring when a person has suffered a serious crisis but has no immediate way of putting it right.

Low self esteem appears to be the common feature behind all four vulnerability factors, and this is perhaps the most important point behind the sociological model. It is not the loss itself that is important but the capacity of the individual to believe in the future; in response to a provoking event they are most likely to feel a sense of hopelessness if they have low self-esteem. If this develops into a general hopelessness then this can form the central feature of the depressive episode. Self-esteem is also important in that it allows the person to go through a proper grieving process and therefore complications leading to depression are less likely to arise. Brown strongly emphasises the cognitive aspect of depression (see Chapter 3) arguing that perceptions of abandonment lead to psychotic symptoms, whereas perceptions of rejection and failure lead to neurotic symptoms. Brown and Harris's findings in Camberwell and the Outer Hebrides have been confirmed by closely replicated studies in Oxford, Sheffield and Calgary. Some recent research by Garnefski and co-workers (1990) has expanded the idea of low self esteem being very important in the development of depression. They found in a group of women aged 22 to 64 years that difficulties in recent and present relationships with parents, partners and others and low self esteem were all likely to predict that the depressive episode would be severe. They also found that experience of physical or sexual abuse before the age of 19 was strongly associated with the severity of depression. Undertreatment of depression in adolescents is now being recognised together with the implications for the future of the individual if the episode is not treated (Keller *et al* 1991).

Diagnosis of depression

A major pitfall in the treatment of depression is the problem of accurate diagnosis and this also compounds the difficulties encountered in research in this area. For a diagnosis to be useful, it must make a statement about the patient's condition such that treatment selection, prognostication and communication are facilitated. The strongest argument in favour of rigid diagnosis is that as treatments become more selective, more restrictive diagnostic

groups are needed, (although this argument is obviously rather a circular one). Researchers in particular tend to prefer very narrowly defined categories in an attempt to reduce heterogeneity within their studies, consequently ; new sub-types of depression continue to be "discovered" e.g. recurrent brief depression (Angst *et al* 1990). However, rigid categories can only be truly useful if they are correct , and the problems that occur in accurate diagnosis of depression are enormous (Rush 1990). Many psychiatrists now use the DSM-III-R (American Psychiatric Association 1987) or the Research Diagnostic Criteria - RDC (Spitzer *et al* 1978) but even with these, sources of variance are high. Subject variance can arise from a specific patient having different diagnoses at different times. Occasion variance can arise if a patient with the same underlying condition presents with different symptoms on different occasions. Information variance can occur when diagnosticians obtain information from two different sources or ask different questions of the same source. Observer variance, is perhaps the most important, and occurs when two clinicians observe the same information or data differently. Criterion variance occurs when clinicians gather the same data but render different diagnoses because they use different criteria. For example, some patients with schizoaffective disorder according to RDC will be diagnosed as having psychotic depression with mood incongruent features by DSM-III-R.

If one looks at the use of self-administered rating scales, then problems of observer variance are immediately removed. The reliability of these questionnaires to give an indication of the severity of the disorder is good, for example the BDI (the Beck Depression Index - designed to measure depression) when compared with a clinical diagnosis has been shown to have correlation coefficients of 0.6 to 0.74 (Feightner and Worrall1990). The BDI is also a good marker of change in a patient and therefore allows monitoring of the patient to take place without the intervention of a physician.

The essential features of an episode of depression are either depressed mood (often seen as irritability in adolescents and children) or most commonly, and most significantly anhedonia. The symptoms will represent a change from the previous functioning of the individual and they will be relatively persistent.

The appearance of depressed patients is often changed in a very characteristic fashion. Dress and grooming may be neglected. The facial features are often characterised by a turning downwards of the corners of the mouth and by vertical furrowing of the centre of the brow. The rate of blinking may be reduced, shoulders bent and gaze averted downwards with minimal gestural movements. However it is very important to stress that many patients show no outward signs and will deny feelings of depression. They may instead present with a variety of different symptoms and will need extensive and very sensitive interviewing to determine the underlying condition. Psychomotor retardation is frequent- although some patients may be agitated. The overall mood of the patients is one of misery which does not improve under circumstances which would normally be expected to elevate mood. The mood is often different from normal sadness - many patients speak of a black cloud pervading all mental activities. Patients will often conceal this mood from other people, due to the fact that depression is still socially unacceptable, and this makes it very hard for a doctor to detect.

Anxiety is very commonly associated with depression particularly in the less severe cases. Agitation and irritability often accompany depressive episodes sometimes in conjunction with loss of energy, this combination of symptoms can be very confusing for the observer. In a recent study, Zung *et al* (1990) found the comorbidity of anxiety and depression to be as high as 67%.

Pessimistic thoughts ("depressive cognitions") are important symptoms which can be divided into three groups. The first group is concerned with the present. The person sees the unhappy side of every event, feels he or she is a failure and lacks confidence. The second group of thoughts is concerned with the future. The depressed patient expects the worst from everything, he or she may feel that life is no longer worth living and may even contemplate suicide. The third group of thoughts are concerned with the past. They often take the form of unreasonable guilt and self-blame about minor matters. Preoccupations of this kind strongly suggest depressive disorder.

A group of symptoms often termed "biological" are extremely important. They include

sleep disturbance, diurnal variation in mood, loss of appetite, loss of weight (or sometimes excessive weight gain), constipation, loss of libido and among women, amenorrhoea. These symptoms become more common with increasing severity of the illness.

The extent of the problem

The vast majority of patients suffering from a depressive episode will be treated by their general practitioner, and certainly the patients seen by the Open Centre which were involved in the following piece of research, would fall into this category. Relatively very few patients are actually referred to a psychiatrist and still fewer are hospitalised. In view of this I shall concentrate on the incidence of depression as seen by the General Practitioner.

Community surveys of the prevalence of depression have generated estimates of 3.5-27% (Prestidge and Lake 1987; Weissman and Myers 1978 a and b). Clearly such estimates are affected by the choice of criteria defining depression, the population studied, the assessment methods and the time scale. As early as 1947 (Watts 1947) , attention was drawn to the problem of depression in general practice, 'endogenous depression' being much more common than was previously appreciated. The problem in assessing the incidence of depression often lies in the definition of caseness (i.e. at what point a set of complaints becomes serious enough to be considered epidemiologically, sociologically or clinically significant) and this has made interpretation of studies difficult. Determining the appropriate cut-off points for case identification to allow detection of milder disorders is thus an incredibly complicated task. A well known study by Shepherd *et al* (1966) found that within a range of London practices 7% of men and 13% of women "usually felt unhappy", 2% and 6% respectively "felt so unhappy that they wished they were dead", 1.8% and 2.5% always "felt miserable and blue", and 2.7% males and 4.4% females "felt life was entirely hopeless". Their pooled practice figures for all forms of psychiatric illness in their sample revealed a total prevalence rate of 140 per 1,000 persons at risk with female cases predominating in a ratio of nearly two to one. Over the last decade our understanding of the epidemiological features of depression has considerably improved. And it now appears that between 15-30% of adults experience clinically significant depression at some

point in their lives. Many studies use the definition of a cut off score on a psychological questionnaire e.g. Nielsen and Williams (1980) using the BDI found 19.8% of patients scored above 10 on the BDI, Zung *et al* (1983) used the Zung Self-rated Depression Scale (SDS) and found 13.2% scored above 55 and Hankin and Locke (1983) found 21% of patients scored above 16 on the CES-D. As this evidence shows, the experience of depression is itself a common one in the primary care situation. However it must be stressed that further examination of such patients shows that only a small proportion of them fulfil diagnostic criteria for depressive disorder as defined in DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders). The Epidemiological Catchment Area study (Regier *et al* 1984), involving over 18 000 people, identified a 6-month prevalence rate of 2.2-3.5% for major depression. This really highlights the point made in the opening part of this chapter, that it is society who dictates what is and is not normal, after all if so many people are affected then is it "abnormal"?.

The reliability of epidemiological studies in general practice has been greatly enhanced by more rigorous definitions of caseness due mainly to the provision of structured interview and diagnostic instruments such as the Present State Examination (PSE) (Wing *et al* 1974) and the Research Diagnostic Criteria (RDC) (Spitzer *et al* 1978). Nevertheless these tools are far from perfect and fail to account for the GP's opinion on the patient's personality, physical illnesses and other important axes which will exert a strong influence on the physicians normal case-making decision.

More reliable studies of depressive disorder which avoid the problem of case definition by GP's include those of Wright *et al* (1980) and Nielsen and Williams (1980). Wright reported a high rate for RDC depressive disorder of 17% of consulting patients. Nielsen and Williams found that 10% of consulting patients fulfilled the diagnosis of 'Depressive Neurosis' (DSM-III). Another study by Casey *et al*(1984) revealed a figure for overall psychiatric morbidity of 7% - roughly half that found by Shepherd *et al* in 1966. Many clinicians have expressed the opinion that these figures are too low and represent the fact that many patients go unrecognised.

Many GPs have their own ways of defining caseness and labelling disorder (Clare 1982). In particular, many GP's resort to the notion of a disorder's 'understandability' in defining caseness, e.g. life events, social problems, relationship difficulties. The role these social factors play in the context of depression is complex and very poorly understood (Jenkin and Shepherd 1983) particularly in the GP setting. It is in this area that the psychotherapies concentrate, by identifying causes of the depression, allowing the patient to understand them, and showing the patient how to overcome them. It is perhaps for this reason that psychotherapy is most commonly regarded as a means of relapse prevention in recurrent depression than as an acute treatment (Miller *et al* 1989).

Epidemiological studies, by their very nature, require a high recruitment if questionnaires such as the General Health Questionnaire are to be used. The reason for this is that primary care patients are usually the most reluctant to participate in questionnaires and interviews, and those least willing to participate are very likely to be suffering from some sort of emotional distress e.g. bereavement or psychiatric disorder (typically alcoholism, personality disorder and major depression). Their non-inclusion therefore exerts a powerful influence upon prevalence rates.

The definitive epidemiological study in primary care remains to be done due to the many methodological problems outlined above. However we can be sure that depression is a common, debilitating, often misunderstood disease, and as I shall demonstrate later one requiring more methods of treatment particularly for patients who suffer relapses.

Concern has been expressed that the incidence of depression is increasing and that the world is entering an age of melancholy (Jablensky 1987)

Sociodemographic factors

Exposure to general practice tends to give the impression that the majority of depressives are young, working class women, but this may be due to to the fact that young women are over-represented in this setting. Tischler at al (1975 a and b) reported that single,

unemployed people, living on their own were the greatest user of general practice services when compared with other groups from the general population from which they were drawn. Marks *et al* (1979) demonstrated that doctors are more likely to detect psychiatric disorder in women than in men. Henderson (1981) showed that depressed people tended to devalue or underestimate the true nature of their supportive relationships. Few studies have controlled for other variables, although interestingly it appears that marriage increases the likelihood of a depressive episode in women, and decreases it in men (Hallstrom 1973: Radloff 1975). Three factors - gender, age and socioeconomic status, appear to be very important in the incidence of onset of depression.

Gender:- Almost all studies of depression conducted in general practice report a gender distribution in which women outnumber men. General population studies report a gender ratio for various depressive disorders of approximately 2:1 (Robins *et al* 1984, Myers *et al* 1984) although in the general practice setting this is higher e.g. Sireling *et al* (1985). General population studies have shown that men are less likely than women to seek professional help when depressed (Weissman and Klerman 1977, Roberts and Vernon, 1982). Why women show a higher incidence of depression than men is not clear although it may, in part, be due to poorer treatment outcome, particularly in older women (Sargeant *et al* 1990). It may also be wrong to particularly identify women as being at risk from depression, there may also be a tendency towards sexism in diagnosis or it may be simply that men show it in different ways e.g. through violence or substance abuse, thus earning a label of personality disorder.

Age:- Depressive illness has traditionally been considered a disorder of middle-age and onwards. for instance Dunn and Skuse (1981) found that women became progressively more likely to consult for depression as they grew older and that they were less likely than men to recover once depressed. However Mazer in 1967 noted that the peak age group for women complaining of disorders which were predominantly psychoneurotic in nature was 25-34 years (men peaked about a decade later). Other primary care studies have supported the view that younger females seem to be especially at risk from depression (Porter 1970; Berndt *et al* 1983; Sireling *et al* 1985) Several studies in the general population indicate that

young adults have more symptoms of depression and symptoms of a greater intensity than older age groups (e.g. Craig and Van Natta 1979; Weissman *et al* 1981; Robins *et al* 1984). This has led to a need for greater examination of the processes of mental development in young adults and adolescents (Burke *et al* 1990).

In an elderly population depression is most likely to occur with advancing age, although other factors such as loss or serious illness of a partner, being alone, few hobbies and poor social participation are very important (Pahkala *et al* 1991)

Socioeconomic status:- Numerous studies have shown that the single most important predictor of score on a self report questionnaire was socioeconomic status. The higher the status or educational level, the less likely the person was to describe themselves as depressed (e.g. Nielsen and Williams 1980: Wright *et al* 1980; Robins *et al* 1984). Symptoms of depression are commonest in the lower social classes, but bipolar depression appears to be commonest in the upper social classes (McCormick 1989).

Recent research by Sargeant *et al* (1990) has shown that the factors that are most likely to predict a poor treatment outcome are, high rates of relapse, chronicity and poor psychosocial environment. They did not find any evidence that sociodemographic factors could influence the outcome of a depressive episode once it had started. Other research, however has indicated that the number of previous episodes is not predictive of outcome (Gurguis *et al* 1990)

Treatment of depression in general practice

Given that depression is such a common problem, it is not surprising that most depressive illness is dealt with by the family practitioner, despite the fact that the GP is often ill equipped to deal with it. As early as 1966, Watts suggested that a motivated GP should be able to treat 90% of his depressed patients at home, emphasising that this was not only less costly than specialist care, but far better for the patients as it enabled them to maintain important ties with the family and community. Depressed patients often experience

difficulties in their relationships with others, and it is an important part of any healing process that they learn to deal with this aspect of their life.

The mainstays of therapy have been tricyclics, Monoamine Oxidase inhibitors (MAOI's), "new generation" antidepressants and psychotherapy. Tricyclic antidepressants have long been considered to be effective and to decrease at least to some extent the risk of early relapse (Rogers and Clay 1975: Mindham *et al* 1973) Similar support exists for monoamine oxidase inhibitors (Robinson *et al* 1973), but the potential side effects have limited their use. Psychotherapy, although widely practised and generally accepted as being effective, is more difficult to study, and the results of these evaluations are often very hard to interpret compared to drug trials. Most reviews of randomised controlled trials and meta-analyses, however, do support the effectiveness of psychotherapy (Weissman 1979: Steinbrueck *et al* 1983). Combined treatment with antidepressants and psychotherapy may produce better outcomes than either treatment alone (Beck *et al* 1985: Teasdale *et al* 1984: Blackburn *et al* 1981).

Recent concern in both the medical journals and the popular press of apparent over prescribing of psychotropic medication has lead to increased public awareness of the possible side-effects of these medications. Although tricyclics, MAOI's and the new second generation antidepressants have broadly equal efficacy, they vary in their side effect profile and potential toxicity (Rudorfer and Potter 1989; Schulz and Dick 1989; Paykel 1988; Baldessarini 1989). GPs are often criticised from within their own profession by psychiatrists, who accuse them of using antidepressants and anxiolytics in an inappropriate manner (e.g. Weissman *et al* 1981) or at sub-therapeutic doses (Parish 1982). In defence of the GP it should be pointed out that prescribing of psychoactive drugs to patients who are otherwise still leading normal lives is a very fine balancing act.

Given that antidepressants are so commonly prescribed how effective are they, and do the benefits out-weigh the risks? Published placebo controlled studies of antidepressant drugs are rare and many show no greater efficacy for the active medication than placebo. For example Gomez and Gomez (1988) and Porter (1970) were unable to demonstrate

significant efficacy of 75mg Amitriptyline or 75-150mg Imipramine respectively over placebo. However Hollyman *et al* in 1988 found that whilst 75mg of Amitriptyline was ineffective, 160mg was efficacious. More recent work by Thompson and Thompson in 1989(a) showed that low dose dothiepin (75mg/day) had no significant advantage over placebo, indeed on measures of depression and somatic symptoms, the placebo patients that completed the trial were more greatly improved. An important point to note at this stage is the difficulty in ascertaining efficacy in trials of this kind. As previously mentioned the diagnosis and assessment of depression is extremely vague and can result in small differences being lost due to huge individual variation.

Many studies indicate greater efficacy at higher doses, however many psychoactive drugs have unpleasant and even lethal side effects. The majority of patients will recover from depression whether or not they are treated with antidepressants, therefore it is important that these drugs are used carefully and discriminately. A physician must consider carefully the side-effect profile and the overdose toxicity of a drug when deciding what to prescribe. For instance the older tricyclics such as amitriptyline should be used with caution in patients with ischaemic heart disease. They also have pronounced anti-cholinergic side effects such as dry mouth, sweating, postural hypotension and tachycardia. The antihistaminic actions of some antidepressants result in sedation (e.g. amitriptyline, mianserin, dothiepin) which has been proven to reduce the patients ability to drive and increase the likelihood of the patient having an accident at home or work. This obviously causes problems for the GP patient and may result in non-compliance (e.g. Thompson and Thompson 1989b). New antidepressants are continually being developed and a whole host of 5-HT uptake inhibitors are now being marketed. These include paroxetine, fluvoxamine, sertraline, citalopram and fluoxetine, they are as effective as the traditional tricyclic medication but lack anti-cholinergic side-effects (Aberg Wistedt 1989; Dechant and Clissold 1991; Langdon 1991;Harris *et al* 1991; Ottevanger 1991a; Smith and Dunbar 1991; Laruelle *et al* 1991) and may also be effective as longterm preventative treatment for recurrent depression (Jakovljevic and Mewett 1991) and have limited effects on psychomotor function (Kerr *et al* 1991). However they may have a whole new side-effect profile of their own, fluoxetine has been implicated in suicidal ideation, although in

depression this is difficult to prove (Creaney *et al.* 1991; Ottevanger 1991b) and also in acts of violence (fluoxetine prescription is being used as a defence by American lawyers in murder cases).

A major consideration in the treatment of depression is that of all the affective disorders, treatment failure is most likely to result in deliberate self-harm (e.g. Urwin and Gibbons 1979) . A number of studies have indicated that many people who attempt or commit suicide have had contact with medical services, particularly GPs, shortly before their attempt or death. (e.g.Turner, 1982; Skegg *et al*, 1983; and Diekstra 1984). The use of antidepressant medication as a primary therapeutic agent to alleviate suicidal ideation has been advocated by some authors (e.g. Goldney and Pilowsky 1980). However there is very little evidence that antidepressants can decrease suicidal behaviour in the clinical setting (Hirsch *et al* 1985; Montgomery and Montgomery 1982; Adam *et al* 1983), although Montgomery *et al* (1983) found a small benefit of flupenthixol over placebo and Ottevanger (1991a) has also claimed similar efficacy for Fluvoxamine. The danger of indiscriminate prescribing of psychotropic medication without a proper assessment of the suicide risks are enormous. The toxicity of antidepressants even in moderate overdose is high (Henry 1988; Beaumont 1989), where death occurs it is normally the result of depressed myocardial function (Dziukas and Vohra 1991). The difficulty of prescribing is that the potentially suicidal person is being given the means to commit suicide, Lundberg (1982) likened the prescription of such drugs "to giving a homicidal man a loaded revolver". A recent survey in the Netherlands showed that 36% of suicides and 64% of suicide attempters used their antidepressant drugs (either alone or with other medication or methods) as the means of committing or attempting suicide (Diekstra and Van Egmond 1989). Some tricyclics are considered to be safer than others, but there is little evidence for this. In particular dothiepin is often quoted as relatively safe. In fact the number of fatal poisonings per million prescriptions with dothiepin is around 50, slightly more than with amitriptyline. Dothiepin, amitriptyline, dibenzapin and desipramine have the highest fatal toxicity indices (Cassidy and Henry, 1987). New generation antidepressants are much safer in overdose (approx 13 deaths per million) and have roughly equal efficacy, therefore one would expect that prescription selection would favour these drugs. In actual fact

current surveys suggest that imipramine, amitriptyline and dothiepin are the most widely used antidepressants (Thompson and Thompson 1989b) presumably mainly due to their low cost. If suicidal deaths were considered an adverse drug reaction and actually reported to the Committee of Safety On Medicines (CSM) there is no doubt that drugs such as dothiepin would be withdrawn. Nomifensine was withdrawn by the manufacturer when 7 deaths from immunoallergenic reactions per million prescriptions were reported (CSM 1986).

A relatively new form of treatment which is gaining popularity for the treatment of seasonal affective disorder (SAD) is bright light therapy (Wirz-Justice 1986). Seasonal affective disorder is a recurring depressive illness induced by the change of seasons, generally into winter, but bright light therapy does not appear to be effective for non-seasonal depression (Mackert *et al* 1991). There is an extensive literature and these data are reviewed elsewhere (Terman *et al* 1989).

There has also been some success using 40 hour sleep deprivation (Roy-Byrne 1984), however with the possible exception of use with concurrent antidepressant medication (Baxter *et al* 1986) patients usually arise from their first night of sleep in a relapsed state (Wehr *et al* 1988). What does seem possible is that in predisposed individuals some factor associated with sleep may be partly responsible for the induction of a depressive episode (Southmayd *et al* 1990). This theory is also supported by the fact that some antidepressants (e.g. imipramine) can dissociate components of circadian rhythms (Wirz-Justice and Campbell 1982), and deliberate dis
sociation of circadian rhythms using sleep deprivation appears to improve mood in about 60% of subjects (Szuba *et al* 1991).

In summary, it appears that depression is a common, sometimes fatal disease which, in many patients will recur. The drug treatment options available are low in efficacy and can be highly toxic, psychotherapy represents a safe alternative to drug therapy but its efficacy is often questioned and the costs are high in terms of time (up to 2-3hours per week), person-power and facilities.

CHAPTER 3

PSYCHOTHERAPY-MAIN TECHNIQUES

The three main types of therapy that were used during this study were encounter, bioenergetics and Gestalt. However it is important to note that therapists at the Open Centre have a a wide range of experience in many techniques and each therapist tends to use an eclectic mix to suit the needs of the individual or the group. Cognitive psychotherapy and behavioural psychotherapy, although not offered by any of the therapists nevertheless form an important part of psychotherapy in Britain and much research has been done on the efficacy of these psychotherapies. The National Institute of Mental Health (NIMH) in the USA recently completed a huge collaborative research programme on the treatment of depression (Elkin *et al* 1985,1989). The therapies investigated were interpersonal therapy, cognitive behaviour therapy, imipramine hydrochloride plus clinical management, and placebo plus clinical management. Patients from all treatment groups improved over the 16 week treatment period. Although there was an ordering of treatment efficacy at the end with imipramine doing best and placebo worse, when the severity of the presenting illness was taken into account there was no difference between imipramine and the two psychotherapies. For the least severely depressed patients there was no difference between any of the four treatments (including placebo). The outcome of this research is likely to be an increasing focus on the treatment of depression with psychotherapy alone or in combination with antidepressants (Klerman 1989) especially when the safety aspects of antidepressant use are considered. The importance of the psychotherapies in relapse prevention seems particularly promising (Shaw 1989).

It is important to stress that the Open Centre is a growth centre and does not exist merely for people with a clinically significant level of psychiatric disorder. However for the purposes of this study it was requested that the therapists present only those patients showing clear signs of a depressive disorder.

It is not the aim of this research to review or comment on the relative efficacy or value of

the different psychotherapeutic techniques, however in order to put the work into context I shall briefly outline the principles of each theory, but will not describe details of their practice as they are very variable depending on the individual and the therapist. In addition I shall devote a small section of this chapter to a description of primal therapy. Although primal therapy did not form any part of the treatment of these subjects it was used in the pilot study to this research.

1. Bioenergetics

Dr Alexander Lowen, the founder of bioenergetic therapy began his first workshop in London with the words 'Bioenergetics is a psychotherapy which seeks to harmonise the body and the mind'. Bioenergetics originated in 1958 but did not come to London until 1975. Bioenergetics, in common with many other psychotherapies sees human problems as having their origins very early in life. It is the conflicts that occur in the present connecting with past events that manifest in a variety of psychological and physiological disturbances. Bioenergetics sees the physical manifestations of the illness as just as important as the psychological and so attempts to treat both. Bioenergetics does not believe in 'cure' rather it finds a way to let people live with their problems.

Psychological health is to be found in the harmony of mind and body. The energy which the body produces should be used to maintain a feeling of strength, authority and aliveness, it should not be allowed to maintain tensions and defences. Lack of psychological health is indicated by loss of energy, lack of spontaneity, awkward movement and limited self-expression . The site of the trauma in the body can provide the clues for the diagnosis and treatment of the disease.

" A person who doesn't breathe deeply reduces the life in his body. If he doesn't move freely he restricts the life of the body. If he doesn't feel fully he narrows the life of his body. And if his self expression is restricted he limits the life of his body." (Lowen 1975)

According to bioenergetic theory psychological disturbance is acquired early in life possibly

even prebirth (Lake 1981). The theory is that the infant protects itself from psychological pain by tensing its muscles and that if no outlet for those feelings is provided the tension will increase. The result of this is the bioenergetic concept of character armour and leads to five basic structures of character analysis (Reich 1961). The five types of character, which are rarely found singly but are normally mixed are: Schizoid (caused by maternal hostility); oral(caused by abandonment in the first 9 months e.g. during war (Mahler 1975)); psychopathic (caused by an overpowering figure - usually the father); masochistic (caused by the mother smothering the child) and rigid (caused by the experience of a tragedy at 3 or 4 years of age - possibly an early manifestation of Oedipal material when the child's early sexuality is rebuffed by a fearful parent (Whitfield 1988)).

The four main factors involved when working with a client in bioenergetic therapy are:- Character analysis, grounding, breathing and energy. Whatever the presenting problem may be, the critical issue is character structure and this is central to the therapeutic process. If a client presents with depression, that will only be examined in the context of their character structure i.e. the permanent features which are visible in the body, of which the presenting problem is merely a symptom. One of the goals of therapy will be to alter the structure to eliminate tensions and defences and if necessary, physical posture is altered.

The second factor is grounding and this is literally contact with the ground. Lowen (1975) claimed it was more beneficial to work upright in a standing position. In this way the client experiences contact with the ground and discovers the authority to stand for themselves in life.

The third factor is breathing. Reduced or shallow breathing reduces contact with physical and emotional pain e.g. the wince response to painful stimuli. Whilst this is effective for short term relief from pain it can become a learned conditioned response which cuts off our ability to feel stress within our bodies caused by physical and emotional needs. Increasing the breathing increases the contact with the feelings which can be distressing, however if the breathing is developed the feeling is released.

Finally there is the principle of energy. Unlike the other three factors energy is visible in the body, in terms of the colour of the skin, temperature and muscle movement. Where a person is breathing, grounded and tension free the energy will produce a sense of being alive. Where the energy is locked up there will be a lack of vitality.

The ultimate goal of therapy will obviously depend on the type of personality and the presenting disorder. Like many of the psychotherapies the therapeutic style will vary widely with the therapist, however there are three broad techniques which are commonly used; grounding, breathing and discharge.

Grounding, very simply is the process of the client using their legs to make contact with the ground and thereby experience the authority of their own body. This sounds simple but the techniques to achieve grounding require time and patience.

Breathing can be aided using a bioenergetic stool which will produce immense stress on a tense chest and enables the client to release and breathe easily.

Discharge techniques are used for the release of feelings. Singing and shouting, kicking and striking can help to release aggression, hurt and anger. It is also important to be able to harness gentle tender emotions, this is best achieved lying down with the knees raised so that contact with the ground is maintained. There are a variety of techniques which can then be used such as reaching out the arms or vocal cries for help. This can lead to discovery of having been neglected and can result in anger and pain, the therapist must therefore have the training and experience to lead the client through this process of discovery. The art of the therapist is then to assess the appropriateness of exercises and the timing and depth of intervention (Cox 1978).

2. Behavioural therapy

In the early 1950's Skinner first used the term behaviour therapy, but it was not until 1958 that the therapy became popularised by Lazarus. According to traditional behaviourist

principles all behaviours are learnt, and therefore abnormal behaviour is merely the result of faulty learning. The central theme of behaviourism is objectivity, that is it concentrates on the behaviour which can be seen and the environment. Traditionally it did not explore subjective influences or any of the internal problems that may underlie the condition. However Lazarus in 1971 stressed the importance of the individual's perception of the environment rather than just considering the direct influence of external events (i.e. a slight move in a cognitive direction).

The concept of normal vs abnormal as defined by behaviour therapy is determined entirely by the society in which we live. If one steps outside what is considered normal by society by the way in which we behave, then behavioural therapists will act to change that behaviour. Psychological well-being is viewed in terms of the individual's ability to control their environment and good adjustment, interpersonal, social, sexual, work and leisure activities.

Fear of anxiety or panic, avoidance of discomfort and learned helplessness are all situations where the individual loses control of their environment. An individual's behaviour is an index of his or her perceptions of self competence or self efficacy (Bandura 1977). In learned helplessness the individual sees their responses as futile (Seligman 1975) and so will eventually fail to initiate coping responses.

Behaviour therapy is most commonly used in treatment of anxiety and eating disorders. Depression alone does not normally result in behavioural disorders. In support of behaviour therapy work by Lelliot and co-workers (1989) has shown that avoidance can sometimes precede panic. Anxiety disorders are treated in very general terms by first of all behavioural analysis and then exposure to the fearful stimulus. This can be a very gradual or very rapid process (termed Flooding) but should always be therapist-aided until the patient is capable of facing their phobias alone.

Depression is not normally treated by behaviour therapy alone, but may be treated by so-called behaviour/cognitive therapy. Lewinsohn (1974) argued that depressives did not

engage or engaged less often in positive reinforcing behaviours, therefore the treatment aim would be to improve social skills. Seligman (1975) suggested that the depressed individual has suffered from a life-long failure to control reinforcers in the environment. In treatment various techniques such as self-monitoring, self-reinforcing and assertiveness training are utilised.

3. Cognitive therapy

Cognitive therapy is broadly divided into three different theoretical schools of thought. The first is that of Ellis (1962) who drew attention to the role of irrational beliefs in neurotic disorders and developed rational emotive therapy (RET) to change these beliefs systematically. RET is widely used in the USA but has little support in Britain. Meichenbaum (1985) has developed a form of cognitive therapy which concentrates on coping strategies. He uses self-instructions as a means of coping with stressful situations - so called 'Stress Inoculation Training'. Although Meichenbaum's principles are widely used in cognitive therapy they tend not to be used in isolation. The most extensively used and researched form of cognitive therapy in Britain is that developed by Beck (Beck *et al* 1979; Beck and Emery 1985). Beck believes that depression is a form of thought disorder (Beck and Wynnwood 1963;1964) where the patient distorts incoming information in a negative way. From work originally carried out in depression, cognitive therapy is now used to treat generalised anxiety, panic disorder (Clark 1986), hypochondriasis (Salkovskis and Warwick 1986) and eating disorders (Fairburn 1985).

Cognitive therapy makes a number of assumptions about the nature of the human individual.

1) The person is an active agent who interacts with the world around them.

2) This interaction takes place through interpretations, inferences and evaluations that the person makes about the world around them.

3) The results of these cognitive processes are thought to be accessible to the consciousness in the form of thoughts or images, and so the person has the potential to change them.

In the cognitive model of depression, the illness results as a failure in the accuracy of the process of interpretation and evaluation such that the processing is usually biased in a negatively distorted way. This thinking tends to be global, judgmental and absolute. For example a depressed person who sees someone they know in the street who ignores them because they are in some way in distracted, may conclude that that person did not acknowledge them because they do not like them and may take this one step further to decide that no one likes them. Psychological health is seen is seen as a state where the individual can make relatively accurate interpretations of events, but this does not necessarily mean that they will always act rationally.

If primitive thinking is in operation , as in the disease state then a number of what Beck termed "logical errors" are likely to occur, as summarised below:-

1) **Arbitrary inference** - drawing a specific conclusion without any evidence to support that conclusion and possibly even evidence to the contrary

2) **Overgeneralisation** - drawing a general rule or conclusion on the basis of one or more isolated incidents and applying the concept across the board.

3) **Selective abstraction** - focussing on detail taken out of context, ignoring other more salient features of the situation and conceptualising the whole experience on the basis of this fragment.

4) **Magnification and minimisation** - gross errors in evaluating the significance or magnitude of an event leading to distortion.

5) **Personalisation** - a tendency to relate external events to his or herself with no basis for making such a connection.

6) **Absolutistic, dichotomous thinking** - a tendency to place all experiences in one of two opposite categories e.g. immaculate or filthy, saint or sinner. The patient will select an extremely negative categorisation for himself.

(from Beck *et al* 1979)

There is good evidence that depressed patients do in fact distort information in a very negative way (Brewin 1988 Review) whilst anxious patients tend to dwell on information

that is in some way threatening (Mathews and MacLeod 1985; Macleod *et al* 1986)

People with psychological disturbances not only experience problems in the processing of information but they are also prone to frequent disruptive thoughts known as 'negative automatic thoughts'. These are spontaneous and unrealistic thoughts, although they may seem plausible at the time, for instance a depressed person may feel 'I can't do anything right'. Whilst everyone experiences these thoughts on occasion, they are much more common in people with psychological disturbance. In depression there is a so called negative triad formed by the patients view of their self, the personal world and the future. They may see themselves as inadequate, worthless or helpless. The world seems to make insuperable demands on them and interactions are misinterpreted as representing defeat or deprivation. They anticipate further failure in the future and this anticipation interferes with their motivation to try. It is important to stress that Beck does not believe that negative cognitions actually cause the disorder, rather that the primary pathology is in the cognitive apparatus. Beck and Emery (1985) describe predisposing factors such as; genetic predisposition, physical disease, developmental traumas, inadequate personal experience to provide coping mechanisms, and counter-productive cognitive patterns, which are then acted on by precipitating factors. Precipitating factors include; physical disease, severe external stress, chronic insidious external stress and specific external stress (which acts on psychological vulnerability).

Early life events, chronic stress or trauma can lead the individual to the adoption of idiosyncratic beliefs, known as dysfunctional cognitive schemata. For example a depressed person may hold the view that to be happy they must be totally successful, or loved, or never make a mistake. These assumptions may not cause a problem to the individual until a life event occurs which is of particular relevance to them. This is also termed the level of the cognitive unconscious (Kihlstrom 1987) where behaviour patterns and assumptions that were originally conscious cognitive patterns become habits and unconscious. The accessibility of nonconscious emotional memory is such that it may often require situational cues. (Brewin 1989)

The three main goals of cognitive therapy are firstly to relieve symptoms and resolve problems, secondly to develop coping strategies, and thirdly to help modify the underlying cognitive structures in order to prevent relapse. Unlike many other psychotherapies cognitive therapy concentrates on the presenting problem.

The tools of cognitive therapy are highly standardised and brief. Each session consists of a review of the previous session, planning, specific tasks and assignment of homework (Beck *et al* 1979). The cognitive approach works from a position of logic, applying basic logical principles and experimentation to the automatic dogma by which the depressed patient perceives, organises and responds to the environment (Rush 1982). The persistent negative constructs accompanying the depression (e.g. I am a bad person, I am going to fail) are identified, the frequency and circumstances are noted and then the patient is asked to test the hypothesis within certain rules of reason and using evidence gathered from everyday events. To involve the patient at an early stage reading matter on coping with depression is given to them (e.g. Beck and Greenburg 1974) and they are asked to complete weekly activity schedules.

Following on from this cognitive strategies can be used to help the patient in 6 main areas:-

1) Detection recording and review of depressogenic beliefs that are noted in the daily record card.

2) Recognition of the link between irrational cognitions and self defeating experiences

3) Recognition of recurrent themes, such as fear of failure, through helping the patient to categorise their emotions.

4) Correction of perceptions by increasingly difficult task assignments

5) Teaching the patient to find more rational and positive explanations of events

6) Development of more adaptive and gratifying thinking patterns.

The important point to note to note is that in cognitive therapy as with other psychotherapies (Karasu 1977) the therapist is a teacher or shaper. Cognitive therapy is a process of discovery, not persuasion (Young and Beck 1982)

4. Encounter therapy

Encounter differs from most other psychotherapies in not having any one great founder; instead it has been described as having 'grass-roots origins' (Shaffer and Galinsky 1974). Overall, however, encounter groups are characterised by an emphasis on the importance of honest emotional here-and-now relating, and the emotional involvement of group leaders. In Britain encounter therapy lost some credibility in the late 1970's due mainly to a rather unrealistic approach, excessive amounts of group pressure and perhaps most importantly a number of untrained group leaders starting to practise. Encounter groups have now become much more realistic, more connected to real life with less use of group pressure and less extreme emotional expression. (The encounter group at the Open Centre used for this study was led by Mike Wibberley who is well recognised as an encounter therapist).

Schutz (1973) described encounter as seeing people as a unity of mind, body and spirit, and providing the space for them to explore and grow into these three areas. The central concept of encounter is identity which is divided into experience and expression. Experience is an inner aspect with both conscious and unconscious sides, it is from experience that we set the rules of what is, and is not acceptable for us as individuals to do. Expression of identity, like experience, has conscious and unconscious aspects and includes, speech, posture, movement etc.

Experience of identity and expression of identity are very closely inter-related. How we see ourselves will affect how we act towards others and therefore how they act towards us, which in turn affects how we see ourselves. For example if a person experiences that their opinion is often ignored they may cease to bother to give their opinion. If they then modify the way they express their ideas to give their voice more strength and assurance and seek eye contact, they may make their opinion heard. After this has occurred several times people expect to hear that person's opinion and so act differently towards them.

Encounter maintains that each person has responsibility for themselves, that they must make their own choices in the group and say yes to what they want and no to what they do

not want. The most important aspect of encounter therapy is the unity of mind, body and spirit, poorly led groups are in danger of concentrating on physical and emotional expression to the exclusion of mind and spirit. It is vital that emotions are not expressed without thought within the group, as this is both useless and potentially damaging. Encounter could also be described as exploration, as it allows individuals to explore all aspects of their identity and to give them responsible expression. For this reason encounter may be used by a person as a means of 'growth' and not just as a therapy. (Elliot 1976)

The qualities which are aimed for in encounter are: firstly, an adequate sense of self (i.e. a feeling of being in charge of our own lives); secondly, to have a sense of our own personal rights and boundaries; third, the ability to resolve conflicts, both internally and in relationships with others; fourth, a willingness to explore and take risks; fifth, the ability to communicate experience and feelings; sixth, the ability to play (Wibberley 1988).

Depression is a sign of disturbance due to repression of the self leading to impoverishment of the personality and experience. This not only leads to loss of energy and depression but also to acting out which, as it results from a repression of a part of the self, is usually accompanied by anger. This destructive acting can result in guilt, which leads to depression and so becomes cyclical.

Acquisition of psychological disturbance from the point of view of encounter does not result from traumatic events in life, rather it results from how we chose to respond to those events and what conclusions about ourselves we were able to draw. Distortions in identity not only result from traumatic events but also the force of day to day attitudes. The important element is expression of self, where any aspect of the self is denied the result is pain, anger and fear which together result in hate (Edwards 1976).

The goals of encounter therapy are very variable depending upon leadership style, group format, the length the group is intended to run for and the participants of the group. The general aims according to Wibberley (1988) are;-

To increase awareness of self and one's personal style of relating

To facilitate expression of the whole range of emotion

To engender a sense of response-ability, personal power and creativity

To increase skills in personal communications with others

The group should provide a place where clients can remove their social inhibitions and relate as honestly as possible. In order for this to be achieved a balance must be sought between honesty, caring, confrontation and support.

Although the individual style of the therapist leading the group will vary the main therapeutic techniques are as described below. (Wibberley 1988)

1) **Direct feedback** - This is a way in which individuals can discover how they come across to others. Within the group participants are asked to be direct and honest, but to give information rather than to project feelings.

2) **Focus on contact** - Direct contact is encouraged, both verbally (saying 'I-You' instead instead of 'one', 'they') and by eye contact.

3) **Checking projections or assumptions** - By asking the group

4) **Repetition** - Used when an emotional statement is made without apparent feeling. Repetition of the statement can produce the emotional response.

5) **Opposites and exaggeration** - If a person is experiencing very strong emotions that result in a physical response, increasing the physical response may help the person to understand better what they are experiencing.

6) **Act as if** - The person is asked to adopt a behaviour strategy very different to their own and act it out within the group. They may find that people then respond very differently to them and that they actually start to feel like the behaviour they have adopted. This is particularly useful to increase assertiveness.

7) **Vocalisation and movement** - Used when a person has problems expressing an emotion.

8) **Confrontation** - It is important to emphasise that these are not only about expressing anger, they can be positive or negative, intellectual or emotional, rational or irrational.

The role of the group leader is perhaps most complicated in encounter therapy. The nature

of the therapy is such that the leader should be involved as a part of the group, but it is important that he or she is able to separate that position from the position of leader which enables situations such as emotional confrontations to be controlled and therapeutic decisions made.

5. Gestalt therapy

Gestalt was founded by Fritz Perls and his wife and co-worker Laura Perls, and first rose to public attention as a distinctive approach in the early 1950's. Gestalt is based on a holistic view of the individual in their relations with the world around them (Perls 1973; Perls *et al* 1974). It points out that humans do not see the world as individual shapes, but in coherent meaningful configurations or 'gestalts'. At the centre of the Gestalt philosophy is the view that personality is comprised of a number of functions - bodily, perceptual, verbal/ cognitive - that interrelate closely and exist in relation to the environment.

Parlett and Page (1990) quote Perls as saying that 'every individual, every plant, every animal has only one inborn goal - to actualise itself as it is'. In Gestalt therapy psychological health and disturbance are not seen as mental but rather as organismic, they are the result of the functioning of mind, body and spirit (Latner 1974). A healthy person will achieve a balance at the interface of themselves with the environment. Imbalances are perceived as needs, and in a healthy person the most important need for self-actualisation will be dominant. The gestalt comprises the need which is being attended to, 'the figure', from the rest of the conscious life termed 'the ground'. As the need increases excitement is generated which activates the person to satisfy the need, for instance a hungry person will make efforts to get food and eat it. After the need is satisfied the gestalt will dissolve and a new gestalt is formed - this is known as the cycle of awareness, and is described in a variety of forms (Zinker 1977; Hall 1976; Parlett and Page 1990). The cycle represents a healthy functioning process in which a gestalt forms, develops and finally destroys itself.

A block may occur at any stage in the cycle. For instance a block at the beginning may prevent the person identifying a need; a block later on may prevent the person letting go of

what they required from the environment and therefore not allowing them to relax. Obviously incomplete gestalts leave the person dissatisfied. Particular attention is paid to awareness and contact in Gestalt therapy.

Awareness is divided into three zones; self-awareness, world awareness and awareness of what's between. Self awareness is direct experience of feelings, emotions and physical sensations at the time they are felt. World awareness is experienced via the five senses. 'What's between' refers to the persons representation of reality, and includes planning, thinking, daydreaming etc. Awareness is very much 'here and now', it is not the same as intellectual understanding. 'Contact' occurs when the individual is fully in touch with the environment. The Gestalt therapist is an awareness expert, who will actively encourage the person to attend to their own ongoing present experience, and will ask questions such as"How did you feel when you said that?', 'What is happening?'. The questions will begin with What and How to focus attention on specific experiences, not Why which requires explanation. The therapist will work to identify where interruptions in the cycle occur by exploring the persons reality almost on a moment by moment basis. Interruptions in the gestalt may be spotted by a number of minor changes such as adjustment of eye contact or unfinished sentences. When interruptions are spotted the therapist can either intervene or allow the person to continue their story (Polster 1987)

There are four patterns of disturbance at the contact boundary identified in Gestalt theory (Polster and Polster 1973). These are; introjection (taking in from the environment without evaluation), projection (displacing from self into the environment), retroflection (self manipulation rather than engagement with the environment) and confluence (merging with the environment and avoiding separateness). It is the role of the therapist to try and identify these contact boundary disturbances. For instance if a person suppresses laughter in a group session it could be that he has an introjection that it is impolite to laugh, or that others may think him silly (projection). In addition, he is trying to swallow his laughter (retroflection) and conform to others around him (confluence).

Where interruptions occur there is a tendency to resist or stay with the familiar pattern of

interruption. For instance someone who has been taught not to cry will find it difficult if they are suddenly told that this is wrong and that they are allowed to cry. For this reasons a gestalt therapist will not say that the resistance is wrong but should adopt a position of neutrality towards a person changing (Appelbaum 1983).

Experimentation forms a large part of gestalt therapy and although there are no set structures or techniques some experiments have become classics. e.g. the 'empty chair' in which a person may resolve unfinished business with someone, or another part of themselves, by talking to the empty chair. Gestalt can also involve working with dreams, fantasies or art. The techniques of gestalt are widely copied but their use outside the rest of the system is not recommended by practitioners of Gestalt (Yontef 1988).

6. Primal therapy

I shall only describe the principles of primal therapy quite briefly as the subjects involved in this research did not receive any of this type of therapy, and the techniques involved are not used by therapists at the Open Centre. Primal therapy, was however used in the pilot study to this research.

Primal therapy was first described by Arthur Janov in 1970. Twenty years on he has amended his theories slightly, but the broad principles remain the same (Janov 1990). Janov expresses emotional disturbances in terms of "Primal pain". This pain cannot be felt physically but is continually processed by the sub-conscious and goes on forever. According to Janov the most catastrophic pains are early life threatening pains such as those caused by a difficult birth or those felt by an unloved child. Because these pains are so intolerable a system of repression or 'gating' is employed by the brain as a means of self-defence. Gating is a means of controlling the perception of pain, rather than the pain itself. Janov describes this as a physical process whereby electrical impulses from pain neurons are actually blocked and prevented from reaching the higher levels of the brain. The details of this process are described in pseudo-scientific terms by Janov but since the mechanisms of emotional pain are so poorly understood there are a huge number of

assumptions made and the theory is a little incredible.

Janov uses the term 'imprint' to describe the repressed memories which find their way into the biological system and produce distorted functions. These 'imprints' can either be imposed by a single traumatic event, or through the chronic failure to fulfil certain basic needs over a longer period of time. The main point about imprints is that they are most readily formed in very early childhood and our ability to imprint declines rapidly with age.

Neurosis is the result of the person existing as two selfs, the real pained self and the unreal self which is the consequence of repression. Primal theories argue that the neurotic is symbolically acting out their past needs in the present. The unloved child will in later life seek uncaring and aloof partners so that they can continue in the struggle to make themselves loved.

Many imprints however are actually formed either in the womb or in the process of birth. If the mother is very stressed, does not want the baby, drinks or smokes these are all factors which effect the quality of the foetal environment and according to Janov imprint on the brain. The trauma of birth itself is seen by Janov as the greatest source of Primal pain and takes a number of different varieties. A baby that is heavily anaesthetised at birth develops into a slow unresponsive child, a baby that's badly bruised and hurt during birth for no apparent reason may grow up determined to fight injustice and become for example a lawyer.

If the birth is painful and traumatic this will leave the infant with a very negative imprint, this imprint is subject to the gating processes of the brain resulting in suppression of the real self, and neurosis. As a result of these assumptions we have a set of so called "Janovian Laws", as follows:

1) keeping secrets from yourself makes you sick,

2) suffering is healing as long as it is at a level that can be integrated,

3) salvation lies in pain,

4) he who acts it out lasts it out, he who acts it in caves in.

Janov envisages illness as the silent scream, the cure to which is to give it a voice. In primal therapy is it not enough for patients to discuss their early life traumas, rather they must relive them in order to reexperience the emotions. This will involve many patients in reliving their birth and early childhood. Reliving these emotions allows the blocked energy to escape, tears may be shed and the gating mechanism can be broken down. This is obviously a traumatic and painful experience through which the patient has to go, and for this reason is not used by many therapists.

Evidence for the efficacy of psychotherapy

Economical and ethical considerations will always tend to be foremost in the arguments for and against psychotherapy. From the economic point of view psychotherapy is expensive in terms of both the patients time and the time of a qualified practitioner. The patient may have to give up an hour or two from work each week to receive psychotherapy, this means that in addition to the time factor involved they have to admit their psychiatric illness to an employer. Sheperd (1984) wrote that much of the problem for psychotherapy lies in the way it is perceived "an undefined technique applied to unspecified cases with unpredictable results. For this technique rigorous training is required". The definition that he quotes may to some extent be true - but in that case where does pharmacotherapy stand? The explanation that pharmacotherapy can offer for the effectiveness of a wide range of 'efficacious antidepressants' although scientifically based is no more rational and is probably less complete than most psychotherapies. It cannot even be argued that pharmacotherapy defines its population with greater accuracy - if this was so then why is it possible to treat anxious patients with antidepressants? So what of outcome, the assumption must surely be that antidepressants, for example, have undergone rigorous scientific testing for their efficacy whereas psychotherapy has not. This is an interesting point, most trials of psychotherapy are carried out on a single centre with relatively small patient numbers. Drug trials are much larger scale, however a drug recently accepted onto an already overcrowded antidepressant market in the States was Sertraline where only two trials showed the drug to be more effective than placebo, eleven did not. Aveline (1984)

argues that psychotherapy is still a relatively new discipline within the NHS (since 1975) and that the risks of continuing to use pharmacotherapy without psychotherapy will outweigh the costs.

An increasing body of evidence is emerging to support the view that the most effective treatment for depression maybe a combination of psychotherapy with drug therapy (Weissman 1979) in a hospitalised population although cognitive therapy appears to be most effective in the GP population (e.g. Blackburn *et al* 1981). Cognitive therapy alone has been found to be as successful in treating depression as pharmacotherapy in a number of separate studies (Blackburn *et al* 1983,1986; Teasdale *et al* 1984; Murphy *et al* 1984; Beck *et al* 1985; Covi and Lipmann 1987) and others have found it to be more effective (Rush *et al* 1977) . Behavioural therapy either in combination with pharmacotherapy or on its own is superior to drugs and leads to lasting improvement (McLean and Hakstian 1979; Wilson 1982; Marks and 0'Sullivan 1988 review; Miller *et al* 1989). However not only behavioural and cognitive therapy have comparable efficacy to pharmacotherapy, similar results have been found with interpersonal therapy (Weissman 1979) self-control therapy (Roth *et al* 1982) and social skills training (Bellack *et al* 1983) The overall view now appears to be that psychotherapy in general, used with drug therapy is considered an effective treatment option (Gastpar 1989) and may help in the prevention of relapse (Miller *et al* 1989) However there has been some criticism of the levels of drug treatment given in comparative studies, which it is argued has biased the results in favour of the psychotherapies (Meterissian and Bradwejn 1989). Meta analysis (the analysis of the results of a number of studies taken together) of psychotherapy studies has not proved particularly useful, Prioleau *et al* (1983) found psychotherapy to be no more efficacious than placebo, whereas Steinbruck *et al* (1983) in an analysis of 56 studies found psychotherapy to be more effective than drug therapy.

Research has set out to compare the efficacy and methods of different types of psychotherapy (e.g. Elkin *et al* 1989), or traditional psychotherapy versus mutual help group treatment (Marmar *et al* 1988) but given the fact that it has not proved possible to detect differences in drug treatments differences in psychotherapies are also likely to be

hard to detect. The result of this work and has therefore tended to conclude, perhaps not surprisingly, that what is called for is an integrative and selective approach (e.g.Karasu 1990a, 1990b). This is also the view of the NIMH study described briefly at the beginning of this chapter.

What is very clear is that no matter how the depressive episode is treated, early intervention is vital (Kupfer *et al* 1989) and can reduce the length of a depressive episode by up to 4-5 months. Fennel and Teasedale (1987) found that the response during the first two weeks of treatment is highly predictive of outcome. The suggestion has been made that the important aspect of psychotherapeutic treatment may be the relationship between the patient and the therapist, rather than the type of treatment (Beckham 1989). Another important factor that has been recognised is the difference between in-patient and out-patient populations and their very different needs in psychotherapy (Kapur *et al* 1988).

CHAPTER 4

SEROTONIN AND DEPRESSION

In 1965 Joseph Schildkraut proposed a theory of depression based on depletion of catecholamines, and also suggested possible involvement of other amines, particularly serotonin (5-Hydroxytryptamine 5-HT). More than a quarter of a century later, despite extensive clinical and laboratory experimentation we are little further in our understanding of the biochemical basis of depression. The original catecholamine hypothesis described by Schildkraut (1965) postulated depletion of noradrenaline at functionally important synapses within the brain, and was expanded to include deficiency of 5-HT, giving rise to the monoamine theory of depression. This theory however falls short due to its inability to explain a number of phenomena associated with the treatment of depression such as: why tricyclic antidepressants have such a slow onset of action, why not all amine uptake inhibitors have antidepressant action (e.g. amphetamine), why different agents with similar pharmacological profiles on the amine system have such different clinical effects and why some antidepressant treatments decrease amine metabolism.

Despite this the popularity of 5-HT and its involvement in depression has remained high, and with the development of a whole new range of highly selective 5-HT re-uptake inhibitor antidepressants the supporting evidence is increasing. 5-HT is an indoleamine, widely distributed through plants, animals and man. In mammals it is found in blood platelets, mast cells and the enterochromaffin cells in the gut. Within the brain and spinal cord 5-HT acts as a neurotransmitter and is thought to be involved in a variety of physiological and behavioural functions. Levels of serotonin in the CNS only represent 1-2% of the total found in the body (Bradley 1989). The indoleamine cannot cross the blood brain barrier and so all neuronal 5-HT has to be synthesised locally. 5-HT is produced from L-tryptophan and metabolised as shown in figure 4.1 below.

Figure 4.1

SYNTHESIS OF 5-HT

L-tryptophan

⬇ L- tryptophan hydroxylase

5-hydroxytryptophan

⬇ 5-hydroxytryptophan decarboxylase

5-hydroxytryptamine (Serotonin)

⬇ Monoamine oxidase

5-hydroxyindoleacetaldehyde

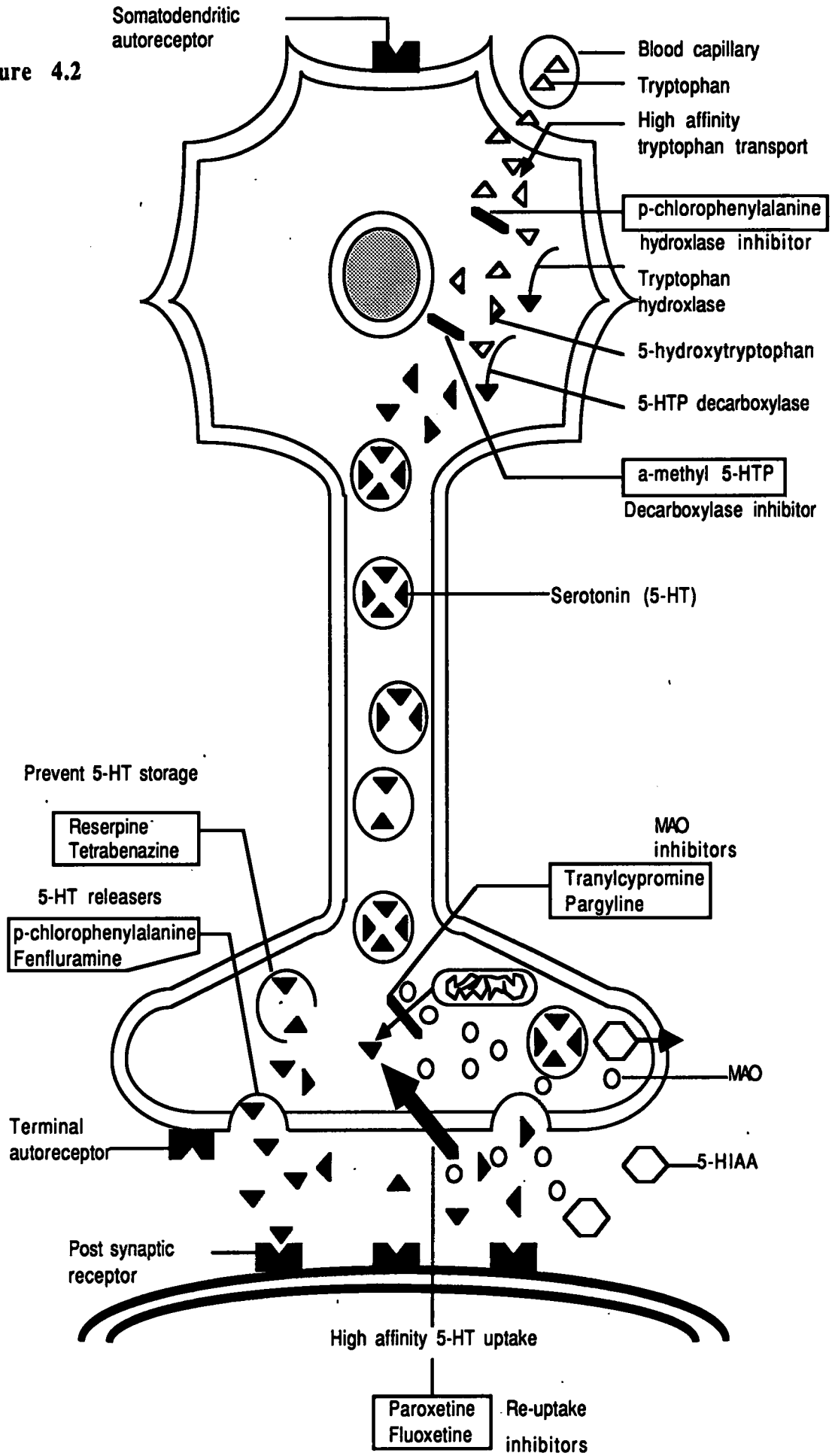
Aldehyde reductase ⬇ ⬇ Aldehyde dehydrogenase

5-hydroxytryptophol **5-hydroxyindoleacetic acid**

The rate-limiting step in this process is the hydroxylation of tryptophan by tryptophan hydroxylase. As under normal physiological circumstances the enzyme is not saturated, increasing brain tryptophan will increase synthesis of serotonin. This has led to L-tryptophan preparations being given orally to patients for treatment of depression with some success (e.g. Zmilacher *et al* 1988). However, overall the results have been equivocal, although, it has been established that tryptophan potentiates the antidepressant effects of monoamine oxidase inhibitors (Coppen and Swade 1988). In addition there have been several other studies which have demonstrated successful use of tryptophan (or another agonist -fenfluramine) challenges to investigate neuroendocrine function (in the form of prolactin release) in normal and depressed patients (Soininen *et al* 1981; Heninger *et al* 1984; Siever *et al* 1986; Cowen *et al* 1988; Goodwin *et al* 1987; Deakin *et al* 1990). A blunted prolactin and growth hormone response to L-tryptophan has been implicated as a possible marker of state dependent depression in patients without recent weight loss (Upadhyaya *et al* 1991) and is reversible with antidepressant treatment (Shapira *et al* 1989).

Within the general scheme of synthesis and metabolism of serotonin there are several stages at which drugs can act to either decrease or increase serotonergic function as shown in Figure 4.2 below. (Drugs acting directly on 5-HT receptors are not included.)

Figure 4.2



(From Marsden 1991)

A number of different lines of evidence suggest that dysfunction of the serotonergic system may be involved in depression. The methods used for studying functional transmitter neurochemistry in the human brain can roughly be divided into three (review by Dodd *et al* 1988). The first is to use human peripheral tissues to study CNS function, the second is to use post-mortem human brain tissue, and the third is to use animal models. All three methods have indicated a possible involvement of 5-HT in depressive disorders

Changes in measures of serotonin function in peripheral human tissues

5-hydroxyindoleacetic acid (5-HIAA) is the final product of 5-HT metabolism within the brain, and its concentration in cerebrospinal fluid is believed to reflect the metabolism of serotonin in the brain. Alterations in the levels of 5-HIAA have been found in a number of studies comparing depressives with control subjects. For example Asberg *et al,* (1984) measured 5-HIAA and two other neurotransmitter metabolites, homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) in the cerebrospinal fluid (CSF) of 83 patients suffering from depression and 66 healthy subjects. The data were adjusted for differences in age, sex, and height distribution between the groups. Significantly lower concentrations of 5-HIAA and homovanillic acid were found in depressed patients compared to healthy subjects, while levels of MHPG did not differ between the groups. Levels of 5-HIAA have also been shown to return to a more normal level after clinical recovery. Traskman-Benz *et al* (1984) were able to demonstrate that concentrations of 5-HIAA , but not HVA, were higher following recovery than during depression, but only in patients with low 5-HIAA during their depressive episode.

Similarly Gjerris *et al* (1987) measured CSF levels of 5-HT in so called endogenously depressed patients and controls and found the concentration in the CSF to be increased in depressed patients compared to healthy subjects. However Molchan *et al* (1991) were unable to demonstrate any differences in CSF monoamine metabolites between depressed patients and controls.

The data tends to support a hypothesis of decreased serotonin turnover in depressed

patients, generally around 40% (Review by Kalus *et al* 1989). The decrease in CSF 5-HIAA could be the result of or could lead to, increased post synaptic 5-HT receptor sensitivity. Kahn *et al* (1990a) tested this hypothesis using MCPP (a $5\text{-HT}_1/5\text{-HT}_2$ agonist) as a probe to detect the effect on behaviour and plasma prolactin levels. MCPP significantly elevated prolactin levels compared to placebo, but there was no difference between depressed subjects and controls. MCPP did not affect anxiety, depression, hostility, fatigue or vigour responses. They concluded that from these findings there was no hormonal or behavioural evidence for increased 5-HT receptor hypersensitivity. These conclusions may be premature, MCPP was given only in single dose, antidepressants acting on 5-HT systems take 2-3weeks to have their effect suggesting that serotonin may act as a mediating system enabling other changes such as down-regulation of B-adrenoreceptors to take place. The effects of MCPP on prolactin release can be reversed using 5-HT antagonists such as metergoline (Kahn *et al* 1990b).

CSF studies are extremely useful in that they enable direct assessment of 5-HT and its metabolites in the fluids that bathe the brain. However there is not any very strong evidence to suggest that these levels particularly closely resemble functional levels of free neurotransmitter within the brain. Furthermore sampling CSF is a highly skilled process and has considerable discomfort and risks for the patient, and for this reason is not a suitable technique for longitudinal studies.

Blood platelets and neuronal synaptic tissue are derived from the same embryonic origins in the foetus and for this reason the surface of the platelet contains a number of receptors also found on presynaptic nerve terminals. In 1951 Rand and Reid reported that blood platelets contained the vasoactive substance 5-HT, however at this time it was not known that 5-HT was a neurotransmitter. The connection with psychiatry was not made until 1960 when Marshall *et al* (1960) showed that patients receiving imipramine had decreased levels of platelet 5-HT. It was subsequently shown that imipramine binds to an uptake site on the platelet, hence stopping uptake of 5-HT and that this uptake site had the same properties as 5-HT uptake sites within the brain (Briley *et al* 1979; Pletscher *et al* 1984; Stahl 1977). Furthermore this site appeared to be specific to tricyclic antidepressants and their active

metabolites (Paul *et al* 1980). Peters and Grahame-Smith (1980) demonstrated that 5-HT actually binds to two specific sites on platelets, one of which is associated with platelet aggregation and the other is associated with 5-HT uptake.

Work on serotonergic function in the affective disorders using platelets has focused into two main areas, that of 5-HT uptake by intact platelets and the binding of 5-HT uptake inhibitors, such as imipramine, to platelet membranes. However it is worth emphasising that platelet receptor binding experiments have also been conducted on other potential psychiatric markers e.g. α_2-adrenergic receptors and monoamine oxidase activity (Wirz-Justice 1988)

5-HT uptake studies

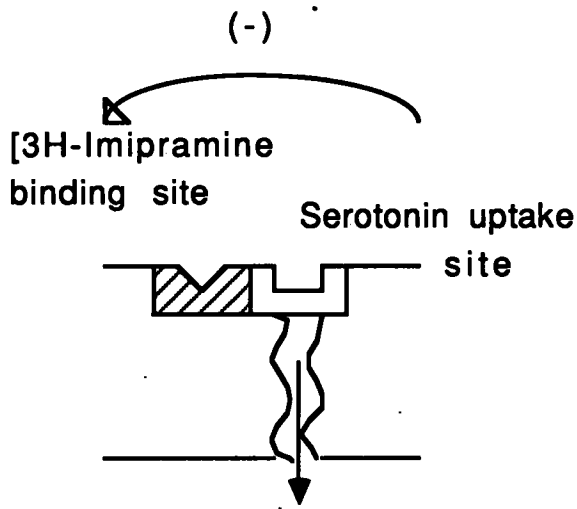
Low values of 5-HT uptake have been consistently found in depression (e.g. Coppen *et al* 1978; Egrise *et al* 1986; Ehsanullah 1980; Hallstrom *et al* 1976; Humphries *et al* 1985; Lingjaerde 1984; Malmgren *et al* 1981; Meltzer *et al* 1981 &1983a; Modai *et al* 1984; Rausch *et al* 1984; Scott *et al* 1979; Suranyi-Cadotte *et al* 1985a; Tuomisto and Tukiainen 1976; Tuomisto *et al* 1979) and appears to be corrected by treatment with antidepressants (e.g. Quintana 1989). 5-HT uptake does not appear to be affected by age or gender (Lingjaerde 1984; Tam *et al* 1985) but interestingly, it has been reported to be increased in manic patients (Meagher *et al* 1990) and treatment of these patients with lithium reduces the rate of 5-HT uptake (Meltzer *et al* 1983b). Additionally levels of 5-HT within platelets of depressed patients are lower than controls (e.g. Muck-Seler *et al* 1983)

However most attention has been directed towards platelet binding studies and in particular the binding of the 5-HT re-uptake inhibitor imipramine. Although imipramine binds to a site associated with uptake of 5-HT, some studies have reported relatively different decreases in 5-HT uptake and imipramine binding. This suggests that although the mechanism of 5-HT uptake and the imipramine binding site are associated, they are not identical (e.g. Raisman *et al* 1982). Langer and Raisman (1983) proposed that the imipramine binding site may be a modulator unit for serotonin and that serotonin and other

uptake blockers change the affinity of this site for imipramine (see Figure 4.3). It seems probable that an endogenous ligand exists which binds to the imipramine recognition site to modulate the 5-HT transporter (Langer *et al* 1987) and that this imipramine recognition site may play a role in the pathogenesis of depression (Langer *et al* 1986).

Figure 4.3

Imipramine binding site



(from Langer and Raisman 1983)

These findings were supported by Marcusson and Tiger (1988) who showed that the imipramine binding site in the brain was localised to serotonergic neurons and appeared to be identical to the substrate recognition site for 5-HT uptake.

Imipramine binding studies:-

Decreased [^{3}H]-imipramine binding to platelets of depressed patients has been demonstrated by a number of investigators (e.g. Asarch *et al* 1980; Asberg and Wagner 1986; Baron *et al* 1983; Briley *et al* 1980; DeMet *et al* 1991; Paul *et al* 1981; Suranyi-Cadotte *et al* 1983 &1985a; Wagner *et al* 1985; Slotkin *et al* 1989) . However there have been a few studies which have either found no difference (e.g. Braddock *et al* 1986; Gentsch *et al* 1984; Tang and Morris 1985; Quintana 1990) or an actual increase (e.g. Mellerup *et al* 1982). Theodorou *et al* (1989) showed decreased binding in female but not male subjects.

In studies where [^{3}H]-imipramine binding has been found to be decreased in depressed patients it has been possible to demonstrate increases in the binding levels following treatment with; some antidepressants (e.g. Asberg and Wagner 1986; Healy *et al* 1983 and 1991; Langer *et al* 1980 Suranyi-Cadotte *et al* 1982 &1985a), light therapy for seasonal affective disorder (Szadoczky *et al* 1989) or ECT (e.g Langer *et al* 1986). Sherwin and Suranyi-Cadotte (1990) were able to show increased imipramine binding to platelets combined with improved mood when oestrogen was given to surgically menopausal women suffering from depressive symptoms. This effect was reversed in a double blind crossover study when placebo was administered. Some research has shown that antidepressant treatment with chlomipramine given to normal volunteers may decrease imipramine binding to platelets (Poirier *et al* 1984) and this led to the suggestion that differences seen in binding between controls and depressed subjects were due to the residual effects of antidepressants. This resulted in a number of investigations into imipramine binding in previously untreated depressed patients, and decreased imipramine binding was still found, showing that this decrease is not the result of antidepressant treatment (e.g. Benkelfat *et al* 1985; Raisman *et al* 1981 & 1982; Poirier *et al* 1986). Wagner and coworkers (1990) investigated changes in imipramine binding to platelet

membranes following treatment with fluvoxamine (a highly selective 5-HT uptake inhibitor) and actually found a decrease in binding sites after 3 weeks of treatment. They suggested that this may be due to destruction of the binding sites, and found that as treatment continued imipramine binding started to increase again. Similar results were also found using clomipramine (Martensson *et al* 1991). It is possible that these findings in some way are related to the high relapse rate seen when antidepressant drugs are only used for short periods and may also explain the increase in severity with subsequent relapses.

Researchers in the field of depression have made considerable efforts to identify both trait (ie some characteristic of the individual which identifies them as a potential depressive) and state (ie some characteristic present when the individual is suffering from the disorder) markers for depression. Not surprisingly, there has been suggestion by some workers that platelet [^{3}H]-imipramine binding may represent a trait rather than a state marker. Baron *et al* (1986) showed decreased imipramine binding to the platelets of bipolar depressives but not unipolar depressives, which led them to suggest that that imipramine binding may represent a trait marker for depression. However other work contradicts this finding, Muscettola *et al* (1986) were unable to show any difference in imipramine binding of bipolar patients and controls. Berrettini *et al* (1982) found that euthymic bipolar patients did not differ from controls in their platelet imipramine binding and concluded that imipramine binding was not a trait marker for affective illness. Imipramine binding has also been proposed as a possible marker of sub-types of depression e.g psychomotor agitation, bipolar depression and sporadic depression (Carstens *et al* 1986a, Lewis and McChesney 1985a) although others have failed to distinguish between subtypes e.g. delusional and non delusional depression (Lykouras *et al* 1988). Jeanningros and co-workers in 1989 investigated further the possibility that platelet [^{3}H]-imipramine binding may be an important trait marker for depression. They concluded that it may represent a trait marker for bipolar disorder and a state marker in dysthymic disorder, as only patients with dysthymic disorders showed a correlation between symptom severity and imipramine binding. What would appear to be most probable is that imipramine binding is decreased during a depressive episode and that the more severe the episode the greater the decrease and therefore the longer the time taken for full recovery. This may therefore be considered

a trait marker for depression in that depression is a cyclic recurrent illness, but it is unlikely that decreased levels of imipramine binding could be used to predict possible depressive disorders in a healthy population with no previous affective disorder.

Other research has suggested that [^{3}H]-imipramine binding might be useful as a possible predictor of response to treatment. For example Hrdina *et al* (1985) looked at binding levels in a group of 20 patients before and after treatment with antidepressants for two weeks and found that patients with the lowest binding levels before treatment were the most likely to be non-responders.

Psychogenic pain also appears to affect imipramine binding in association with depression, resulting in lower imipramine binding in depressed patients suffering from pain than in those solely suffering from depression (Mellerup *et al* 1990). Eberhard and co-workers (1989) monitored imipramine binding in a group of patients with psychogenic pain but no diagnosis of depression and found that they had decreased imipramine binding which increased with antidepressant treatment.

[^{3}H]-imipramine binding has been investigated in a number of other disorders such as panic disorder (Pecknold and Suranyi-Cadotte 1986), Alzheimer's dementia (Suranyi-Cadotte *et al* 1985b; Galzin *et al* 1989), mania (Lewis and McChesney 1985), disruptive behaviour disorders (Stoff *et al* 1991) obsessive compulsive disorder (Won Kim *et al* 1991) and schizophrenia (Joseph *et al* 1977) and since no difference was found between psychiatric patients with these disorders and controls the validity of imipramine binding as a marker of depression seems useful. However Marazziti *et al* in 1989 were unable to demonstrate any differences in imipramine binding between patients with major depressive disorder and patients with bulimia, panic attacks, schizophrenia or suicide attempters. Other workers have found decreased imipramine binding in patients with agoraphobia (Lewis *et al* 1985).

Although imipramine binding is probably not affected by many other psychiatric disorders, this does not imply that serotonin is not involved. Increased levels of 5-HT in platelets has

been observed in schizophrenics (Muck-Seler *et al* 1988) and some studies have shown increased platelet 5-HT uptake (Lingjaerde 1983; Modai *et al* 1979) although others have not (Arora and Meltzer 1982). There is good evidence for the involvement of 5-HT in schizophrenia but interestingly schizophrenics that commit suicide do not appear to have decreased CSF 5-HIAA levels (Lemus *et al* 1990). Serotonin is also implicated in Alzheimer's disease where autoradiographic analysis of post mortem brains has shown a reduction of 5-HT_2 and 5-HT_{1A} receptors in the cortex (Cross *et al* 1988). Eating disorders are almost certainly under some form of serotonergic control (Review Jimerson *et al* 1990) and the role of serotonin in maintaining normal weight is currently under investigation.

Most studies have found no difference in [^{3}H]-imipramine binding between the sexes (e.g. Asarch *et al* 1980). However Langer *et al* (1980) found that there was a decrease in maximal binding with increasing age of the patient and Slotkin *et al* (1989) have reported similar findings of decreased 5-HT uptake with age.

Evidence from human brain tissue for the involvement of 5-HT in depression

There are obvious problems associated with working with human brain tissue, but the usefulness of such studies should not be under-emphasised, as ultimately it is understanding of the human brain in depression that will lead to the answers. One of the greatest problems is obtaining tissue to work on. There is known to be a high prevalence of depression amongst people who commit suicide and so for this reason suicides are often studied in depression. Stanley *et al* (1982) were some of the first workers to investigate imipramine binding to serotonin uptake sites in the Brodmann area of the frontal cortex of suicides. They found decreased levels (44% lower) of imipramine binding in suicides compared to controls. Similar results have since been found in a number of other studies (e.g. Crow *et al* 1984). These results were not however supported by Meyerson *et al* (1982) who actually found increased imipramine binding in suicides or by Arora and Meltzer (1989) who found no difference. Some workers have reported an asymmetrical

distribution of imipramine binding within the brain of suicides although this now does not appear to be the case (Arora and Meltzer 1991).

Pandey *et al* (1990) using ^{125}I-LSD have found that 5-HT$_2$ receptors on platelets are increased in drug free depressed patients and that this is most marked in those that had recently attempted suicide. This finding has also been observed in the pre-frontal cortex of suicides (e.g. Mann *et al* 1986; Meltzer *et al* 1987). Such up-regulation of 5-HT$_2$ receptors is known to result from serotonin deficiency (e.g. Roth *et al* 1987). A review by Mann *et al* (1989) postulates a role for serotonin in suicide where a decrease in the level of serotonin causes an up-regulation of 5-HT$_2$ receptors and a decrease in uptake sites. How this then affects depressive mood and or suicidal behaviour is not clear but a theory put forward by Roy and Linnoila (1988) suggests that serotonin may actually control impulsiveness. They argue that abnormality in serotonin systems has been associated with suicide, particularly violent suicide (Mann *et al* 1986), aggression towards others (Linnoila *et al* 1983) and aggression towards inanimate objects e.g arsonists (Virkkunen *et al* 1987). They argue that whilst these behaviours are multi-determined they all reflect poor impulse control and that this may reflect low serotonin turnover. Coccaro (1989) also argues that the role of serotonin may be to control impulsiveness and particularly impulsive aggression. Sparks and Little (1990) investigated changes in serotonin binding in the pineal of suicides and found that high affinity binding was reduced in some but not all suicides, these results were very preliminary but suggest a possible control role for the pineal via either melatonin, serotonin, noradrenaline or a combination of these. It is worth noting that recent work by Arato *et al* (1989) found that although 5-HIAA levels in the CSF of suicides tended to be lower than controls, if the CSF was examined within ten hours of death increased levels of 5-HIAA were found. Traskman-Benz *et al* (1991) have suggested that higher levels of whole blood serotonin may be associated with impulsive violent suicide.

Although relatively few studies have been carried out on the brains of depressed patients dying from causes other than suicide the findings tend to indicate a role for serotonin. Perry *et al* (1983) compared tritiated imipramine binding to various brain regions in normal, depressed and demented (Alzheimer's type) patient brains post-mortem. They found

decreased imipramine binding in the hippocampus and occipital cortex of depressed patients only. More recently Demeter *et al* (1989) investigated tritiated imipramine binding in the frontal cortex of homicide victims either with or without previous psychiatric illness. The number of imipramine binding sites in the frontal cortex of psychiatric subjects was significantly higher in the left hemisphere than in the right, the opposite was true for the normal controls. They conclude that the significant increase in imipramine binding sites in the left hemisphere may indicate a biochemical lesion of serotonin metabolism and may itself predict psychiatric illness. This experiment however involved a whole range of psychiatric illnesses (alcoholism, depression, schizophrenia, schizo-affective disorder and drug abuse) and only 15 subjects. Given the very different symptomatology and treatment of these diseases, a single underlying cause is improbable.

Imipramine binds to two sites in human brain tissue, one low affinity and one high affinity site, it now appears that only the high affinity sites are related to 5-HT uptake sites (e.g. Plenge *et al* 1990)

Evidence from animal models for the involvement of 5-HT

The use of animal models in investigation of the affective disorders is a highly controversial area. It seems almost certain that animals do not suffer from depression as such, and that the models that we choose to use such as learned helplessness, are in fact models of despair (ie utter loss of hope and extreme stress, in these cases produced as a result of physical factors). What we do not know is whether the mechanisms behind despair are the same as those in depression. Other models induce "depression" using drugs such as reserpine, and are validated in as much as the fact that current antidepressants work in them (Vetulani *et al* 1986). What we do not know is whether or not they are good enough models to have any predictive value for future research.

Work using these models has indicated potential new antidepressants e.g. reversal of learned helplessness in rats by 5-HT_{1A} agonists (Giral *et al* 1988). It could be argued that the usefulness of animals in the study of depression comes from being able to monitor

changes in binding sites in the brain with administration of antidepressants. This may eventually lead to a fuller understanding of how antidepressants work and then, maybe, the mechanism behind depressive disorder. Mizuta and Segawa (1989) investigated changes in different 5-HT receptor sub-types using quantitative receptor autoradiographic procedures in rat brains after chronic administration of imipramine or lithium for 21 days. They found decreases in 5-HT_1, 5-HT_{1A}, 5-HT_{1C} and 5-HT_2 sites in the frontal cortex, hippocampus and choroid plexus for both lithium and imipramine treatment (although in different amounts) and proposed that this technique could offer a means of characterising and understanding the local effects of drugs on 5-HT receptor sub-types. More recent work by Perez *et al* (1991) has shown that both noradrenaline and 5-HT re-uptake blockers with antidepressant activity increase cAMP binding indicating that this may be part of the adaptive change brought about by antidepressant treatment. Electrophysiological assessments of 5-HT neurotransmission in rat brain following treatment with antidepressants has shown that all the antidepressants tested produced an enhancement of 5-HT activity, although each one may have achieved this by a different mechanism (Blier *et al* 1988).

Imipramine binding in human platelet cells has been reported by some workers as being subject to circadian variation, the effect of photoperiod on imipramine binding in the rat brain has also indicated circadian variation (Rovescalli *et al* 1989). Jernej *et al* (1989) however, found no evidence for significant circadian or seasonal oscillations.

Animal studies are useful in order to investigate the localisation of binding of antidepressants within the brain. Rainbow *et al* in 1982 found a heterogeneous distribution of imipramine binding sites in the rat brain. They found little or no specific binding over the white matter, or in the reticular formation and ventral thalamus. They found a moderate amount of binding in several brain areas including the caudate putamen, all layers of the cerebral cortex, and all subregions and laminae of the hippocampus. A high level of specific binding was found in the dorsal and medial raphe nuclei, the interpeduncular nucleus, the superficial layer of the superior colliculus, the locus coeruleus, the dorsomedial nucleus of the hypothalamus and the central grey. They concluded that the

distribution of imipramine binding sites was in close agreement with the distribution of 5-HT terminals in the brain.

The use of animals has also been important to demonstrate the validity of imipramine binding as an marker of changes occurring in the brain. Briley and co-workers in 1982 were able to demonstrate parallel decreases in imipramine binding to platelets and hypothalamus in cats treated chronically with imipramine for 20 days. Evidence from work with pregnant rats is that treatment with antidepressants during pregnancy actually decreases imipramine binding sites in the newborn rats (Montero *et al* 1990).

Further evidence comes from the fact that known antidepressants influence 5-HT metabolism and that 5-HT precursors can improve the condition (e.g. Raba *et al* 1984). Over the last decade increasingly more specific 5-HT uptake inhibitors have been introduced onto the antidepressant market, these include fluoxetine, fluvoxamine, sertraline and citalopram (See Aberg-Wistedt 1989 for review). The fact that they work in a number but not all depressives, suggests an important role for serotonin in depression but also implies that it is not the full picture (Swinson 1989).

Although most of what I have discussed above emphasises the importance of serotonin in depression, it would be wrong to give the impression that the picture is that simple. A major problem with the serotonergic theory of depression is that the serotonin system is linked, both functionally and anatomically, to other neurotransmitter systems, so that alterations will produce changes in both dopaminergic and noradrenergic systems (e.g. Arnt *et al* 1984; Agren *et al* 1986; Sulser 1987; Bijak and Smialowski 1988; Potter *et al* 1988).

Another problem is the huge number of disorders where serotonin related abnormalities have been found; serotonin dysfunction is implicated in schizophrenia (e.g. Le-Quan-Bul *et al* 1984), alcoholism (e.g. Borg *et al* 1985), obsessive compulsive disorder (e.g. Zohar and Insel 1987; Hollander *et al* 1989; Bastani *et al* 1991), panic disorder (e.g. Nemeth *et al* 1989; Targum and Marshall 1989) and eating disorders (e.g. Kaye *et al* 1988; Marazitti *et*

al 1988; Jimmerson *et al* 1989). Decreased serotonergic activity can also be seen in Parkinson's disease and dementias (e.g. Argentiero and Tavolato 1980; Palmer *et al* 1984; Volicer *et al* 1985; D'Amato *et al* 1987; Mayeux *et al* 1988). Decreased 5-HIAA in the CSF is also found in a number of conditions such as infantile spasm (Silverstein and Johnson 1984) and the psychiatric symptoms that accompany hyperparathyroidism (e.g. Almay *et al* 1987; Joborn *et al* 1988). High levels of 5-HIAA have been associated, with among others, hypertension (Sharma *et al* 1985) and sub-arachnoid haemorrhage (Suzuki *at al* 1987). Autism has been linked with a blunted prolactin response to fenfluramine, decreases in platelet 5-HT_2 receptors, decreases in platelet serotonin uptake and increased levels of serotonin in the blood (MacBride *et al* 1989; Rolf *et al* 1989; Launay *et al* 1988). It is rather difficult to explain how one neurotransmitter system can be responsible for so many diverse conditions if we only allow ourselves to refer to simple overactivity or underactivity.

Additionally there has been the failure of a number of studies to demonstrate a relationship between change in markers and clinical change, and also the fact that therapeutic treatments, although effective, may produce different alterations in the serotonergic system. For example antidepressant treatment may decrease 5-HIAA in the CSF (e.g. Bjerkenstedt *et al* 1985) or may decrease the uptake of serotonin into platelets (e.g. Schlake *et al* 1989). The specific serotonin re-uptake inhibitors are therapeutic in conditions where they must apparently exert opposite effects e.g. obsessive compulsive disorder (Goodman *et al* 1989a,1989b) and impulsive aggressive personality disorder (Coccaro *et al* 1989; Cornelius *et al* 1989). In the former 5-HIAA levels in the CSF are elevated (Charney *et al* 1988; Hollander *et al* 1989), in the latter 5-HIAA is decreased (Brown *et al* 1982,1985).

The validity of strategies in serotonin research still needs clarifying. We cannot be certain that levels of 5-HIAA seen in the lumbar CSF actually represent brain levels. Indeed there is some evidence that it may not (Gjerris 1988).

The noradrenergic theory of depression

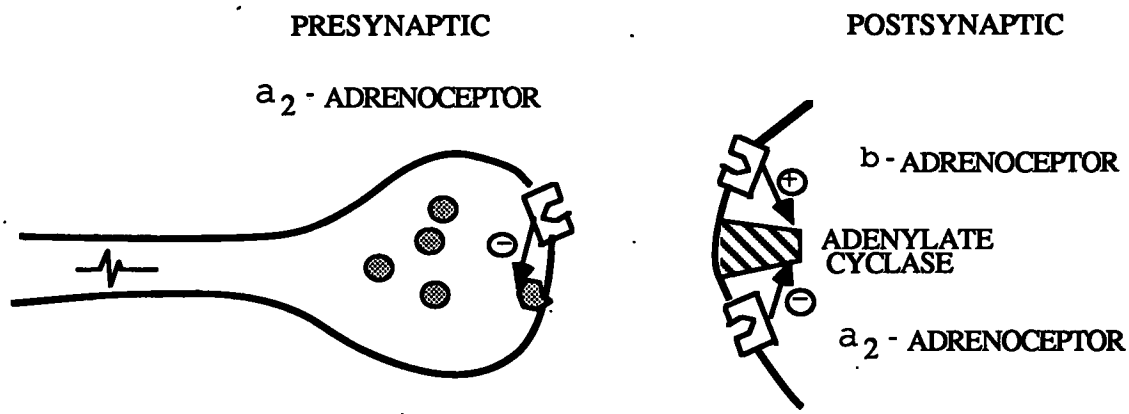
It was originally intended that as part of this research the effect of psychotherapy on α_2–adrenergic receptors would also be investigated. There is considerable interest in the functioning of adrenergic systems in people suffering from psychiatric disorders. Schildkraut (1965) proposed two possible methods by which adrenergic function may relate to depressive illness. The first possibility was that depression was directly associated with decreased adrenergic function and that effective treatment would be to increase adrenergic function and thereby alleviate the symptoms. The alternative was that depression may be associated with a variety of biochemical changes which result in decreased adrenergic function in the central nervous system in an attempt to adapt to the changes. Under these circumstances treatment would need to promote the decrease in adrenergic function rather than oppose it. The former possibility now seems to be the most likely, as down regulation of β-adrenoceptors is seen in depressive disorder (Extein *et al* 1979) and effective antidepressants or electroconvulsive therapy cause an up-regulation of β-adrenergic function and increases in plasma noradrenaline levels (Rudorfer *et al* 1991; Cooper *et al* 1985)

Although current information concerning the role of α_2–adrenergic receptors in depression is far from conclusive it does appear that α_2-adrenoceptor activity is increased in depressive compared to euthymic subjects (Wood and Coppen 1981; Coppen and Wood 1980). This has also been observed in patients with pre-menstrual dysphoric changes (Halbreich *et al* 1989) and in the frontal cortex of depressed suicide victims (Meana and Garcia-Sevilla 1987). The α_2–adrenoceptor under normal circumstances inhibits noradrenaline release into the synapse thereby preventing excess release and allowing levels of noradrenaline to fall between stimuli. As shown in Figure 4.4 increased

α_2-adrenoceptor capacity centrally would reduce adrenergic activity at the synapse as mediated by the post-synaptic β-adrenoceptor. This could be both as a result of increased inhibition of noradrenaline release via presynaptic autoreceptors causing down regulation of β-receptors or resulting from inhibition of adenylate cyclase activity at the post synaptic α_2-adrenoceptor.

Figure 4.4

Noradrenaergic synapse



There are only limited data available on α_2-adrenoceptor binding characteristics in human brain tissue comparing depressed and non-depressed subjects, so it is difficult at this time to assess which radioligand best reflects the central α_2-adrenoceptor changes, if any, associated with depression. However clonidine, a mixed α_2-agonist-antagonist is known to stimulate growth hormone release, via the noradrenergic system and this response can be shown to be blunted in endogenously depressed patients (Charney *et al* 1982; Horton *et al* 1986), even following clinical recovery (Mitchell *et al* 1988). This is suggestive of persistent α_2-hypersensitivity.

In animal models long-term administration of tricyclic antidepressants reduced the a_2-adrenoceptor binding capacity as measured by [^{3}H]clonidine, in specific areas of the rat brain - the amygdala, hippocampus and locus coeruleus (Smith *et al* 1981; Smith and Garcia-Sevilla 1982). However no changes were observed in the binding capacities of [^{3}H]-yohimbine or [^{3}H]-DHE (Campbell and McKernan 1982). Other forms of antidepressant treatment, such as electro-convulsive therapy, have also been shown to reduce [^{3}H]clonidine binding (Pilc and Vetulani 1982; Stanford and Nutt 1982).

A number of different radioligands have been used to label platelet α_2–adrenergic receptors (e.g. Motulsky *et al.* 1980,1982; Shattil *et al.* 1981; Cheung *et al.* 1982; Carstens *et al.* 1986b). Consequent discrepancies in the binding capacities identified by each radioligand constitute a major problem in the interpretation of platelet α_2-adrenoceptor binding studies in depression and may at least in part be due to an apparent heterogeneity of α_2–adrenergic receptors observed in rat brain (Boyajian *et al* 1987; Boyajian and Leslie 1987). In addition there has been some difficulty in obtaining consistent results even using certain of the same ligands. For instance, using the selective α_2-adrenoceptor antagonist [^{3}H]-yohimbine or its

isomer [^{3}H]-rauwolscine, several independant studies have observed no difference between depressed and euthymic subjects in their platelet binding characteristics (Daiguji *et al* 1981; Pimoule *et al.* 1983; Stahl *et al.* 1983; Cameron *et al.* 1984;Campbell *et al* 1985; Braddock *et al.* 1986). There are however conflicting results on the effects of antidepressants on [^{3}H] yohimbine or [^{3}H] rauwolscine binding to platelets in depressed subjects. For instance, Pimoule *et al.* (1983) reported no change in [^{3}H] rauwolscine binding in patients receiving chlorimipramine or amitriptyline for periods of up to 35 days, whereas Braddock *et al.* (1986) found treatment of depressed patients with amitriptyline for 28 to 42 days significantly reduced [^{3}H] yohimbine binding, but they were unable to demonstrate any correlation between this reduction and improvement in clinical condition. Cooper *et al.* (1985) using [^{3}H]-rauwolscine showed a reduction in platelet binding in depressed patients after electroconvulsive therapy but they too were unable to relate this to clinical improvement. Overall the choice of yohimbine-alkaloids for binding to platelet adrenoceptors has failed to produce uniform results in differences between binding in depressed and control subjects (Reviews by Kafka and Paul 1986; Katona *et al* 1987).

Using the non-selective α–adrenoceptor antagonist dihydroergocryptine (DHE), Wood and Coppen (1981;1983) reported fewer platelet binding sites in a group of depressed patients when compared to controls, with no change in binding affinity. In direct contrast to this, Healy *et al.* (1983), using the same radioligand, reported significantly higher binding capacity in depressed patients as compared to controls, and subsequently, in those patients showing clinical improvement the binding capacity fell to a level similar to the controls. However supporting evidence for Healy *et al*'s (1983) results have since emerged and it now appears that DHE may be a useful marker (e.g. Roy and Kafka 1989)

The only radioligand at the time when this research was set up, in which repeated studies had shown significant differences between depressed and control subjects was [^{3}H]clonidine, and for this reason it was the marker of choice for labelling α_2-adrenergic receptors in this study. Shattil *et al.* (1981) demonstrated that [^{3}H] clonidine could be used

to identify high-affinity α_2-adrenergic receptors on human platelets. Furthermore it had been demonstrated that clonidine binds to a different subset of receptors than yohimbine (Piletz and Halaris 1985) and therefore there was a possibility that it may not be as susceptible to the variation in results as discussed above. Binding of [^{3}H] clonidine to the platelets of depressed subjects is significantly higher than that of normal controls (e.g. Pandey *et al* 1989), and furthermore, this binding level is seen to fall in association with clinical improvement following administration of tricyclic antidepressants, lithium or electroconvulsive therapy (Smith and Garcia-Sevilla 1982; Smith *et al.* 1983; Cameron *et al.* 1984). It would therefore appear that [^{3}H]-clonidine binding may represent a state dependent marker for depression, and possibly schizophrenia (Pandey *et al* 1989). It is perhaps worthy of mention at this stage that studies on α_2-adrenergic receptors in depression have concentrated on the so called endogenous subtype of major depressive disorders. To my knowledge no research has been conducted on people with less severe cases of reactive depression such as were to be studied in this project.

Since the setting up of this project the situation regarding markers of alpha$_2$-adrenoreceptors on platelets has been further clarified, with the result that, [^{3}H]-DHE, [^{3}H]-clonidine, [^{3}H]-para-aminoclonidine, and [^{3}H]-adrenaline have all been identified as showing increased platelet binding in depression (Garcia -Sevilla *et al* 1986,1987; Garcia -Sevilla 1989; Doyle *et al* 1985; Kafka *et al* 1985; Roy and Kafka 1989; Piletz and Halaris 1988; Piletz *et al* 1990, 1991; Pandey *et al* 1989; Takeda *et al* 1989). It has been suggested that the reason that these compounds detect differences between depressed and non-depressed subjects may be because these agents label high affinity agonist induced states, whereas yohimbine and rauwolscine at the concentrations used tend to label low affinity binding states. As a result of these findings Garcia-Sevilla *et al* (1986 and Garcia-Sevilla 1989) proposed that only high affinity α_2-adrenergic receptors are elevated in depression. However it should be emphasised that even using these assays differences are not always apparent between depressed and control groups (e.g. Carstens *et al* 1986b;

Theodorou *et al* 1986; Georgotas *et al* 1987). Therefore, the status of platelet α_2-adrenoceptors in depression, remains unclear.

Roy and Kafka (1989) and Siever *et al* (1983) have shown that depressed patients have reduced prostaglandin E_1-stimulated cyclic adenosine 3',5' monophosphate (cAMP) production, and a significantly decreased percentage inhibition of cAMP production by noradrenaline, furthermore noradrenaline levels could be correlated with [^{3}H]-DHE binding where there was adequate PGE_1 stimulation of cAMP (Siever *et al* 1984). Roy and Kafka proposed that there may be a dissociation between α_2-adrenceptor binding and responsivity in depression.

CHAPTER 5

PILOT STUDY

As discussed in Chapter 4 platelets have been used widely as models for neurones in binding, storage and uptake studies. The similarities and differences of the serotonin and noradrenergic systems in platelets and neurones are discussed elsewhere (e.g. Stahl 1985; Pletscher *et al* 1984) as is the relative usefulness of platelet studies (e.g. Dodd *et al* 1988). The most widely used marker has been imipramine binding to platelet membranes which has generally been found to be decreased in depressed patients (e.g. Slotkin *et al* 1989) and this was the marker of choice in a pilot study set up in this laboratory. In the following sections I shall briefly outline the results found in this study as they were the basis upon which the present project was set up and are relevant to the discussion of these data.

Method

As far as I am aware the first work to be carried out investigating changes in biochemical markers in patients undergoing psychotherapy was, carried out by this laboratory in 1984 (Rose and Murphy 1987). The therapy that the individuals were undergoing was a particularly intensive form of therapy known as primal therapy whose theory explains psychic distress in term of traumatic events occurring very early in life, possibly even at birth (e.g. Janov 1990). The treatment of the disorder can involve a re-birthing process and can be, in itself be a very traumatic process (see Chapter 3). A group of 16 volunteers entering a period of primal therapy at Dr Janov's centre in Paris, had blood samples taken 3 days before therapy began, on the day therapy started, on day 21 and 6 month and 12 month (only 8 samples) follow ups. The population had an even sex distribution and was aged between 24 and 45. None were taking any prescribed psychoactive medication during the study.

A control group of similar age and sex distribution was taken from the Open University and blood samples taken on a similar time scale. An **n** of 17 fell to 13 by the 6 month time

point and no 12 month samples were taken.

Therapists were also asked to rate primal subjects on a 13-item assessment scale devised by Janov, on the basis of clinical notes written prior to the start of therapy and at the 6 month follow up. Items were assessed on a 1-4 scale and ranged from anxiety and depression through to concentration difficulties and sleep disorders. These were converted to global scores for each subject for each assessment point (minimum score indicating least distress = 13, maximum score = 52)

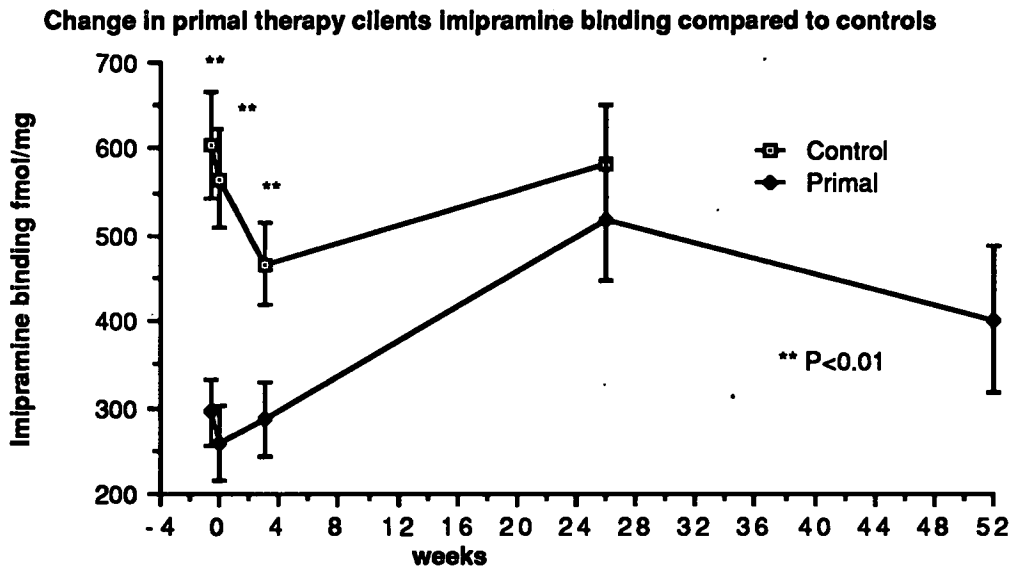
The assay of choice for this study was imipramine binding to platelet membranes. Blood samples were drawn and assays performed using the methods described in Chapter 6.

Results

As can be seen in figure 5.1, the results were very promising. They indicated that self referring individuals entering a period of primal therapy had maximal imipramine binding levels that were approximately half that of a normal control group. Also, six months after starting a course of primal therapy their imipramine binding levels had increased to a level indistinguishable from control levels. Eleven subjects showed an improvement according to the psychiatric assessment scale, and there was a very weak positive correlation between this improved assessment score and increased imipramine binding (see figure 5.2). Interestingly some evidence of circannual variation was seen in imipramine binding in both controls and Primal subjects as had previously been reported elsewhere (e.g. Galzin *et al* 1986). However the pattern of seasonality was very different in primal and control subjects, and may represent changes as a result of the primal therapy in addition to seasonal effects (see Figure 5.3)

Figure 5.1

The graph below shows the change in primal therapy client [^{3}H]-imipramine binding to platelet membranes compared to controls over the 12 month period of the study



Control values:

-3 days **n=17**; 0 weeks **n=15**; 3 weeks **n=16**; 26 weeks **n=13**

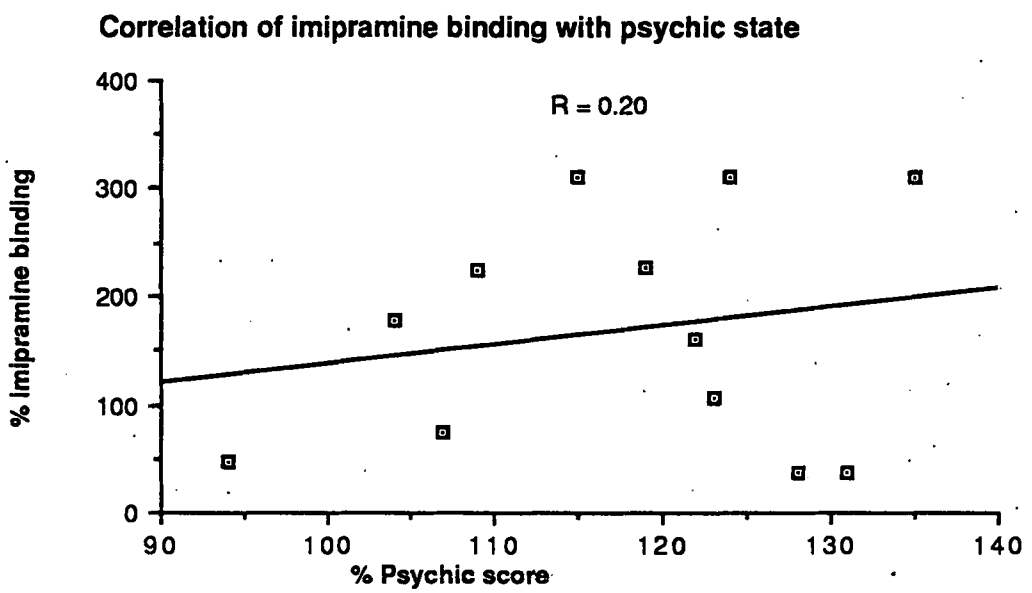
Primal therapy client values:

-3 days **n=16**; 0 weeks **n=14**; 3 weeks **n=13**; 26 weeks **n=14**; 52 weeks **n=8**

Results are expressed as means +/_ standard error of means. Statistical analyses were performed using a one tailed students t-test. The control data being taken to represent the normal population.

Figure 5.2

The graph below shows the correlation between the changes in imipramine binding and the change in the psychiatric rating scales in the Primal therapy clients.

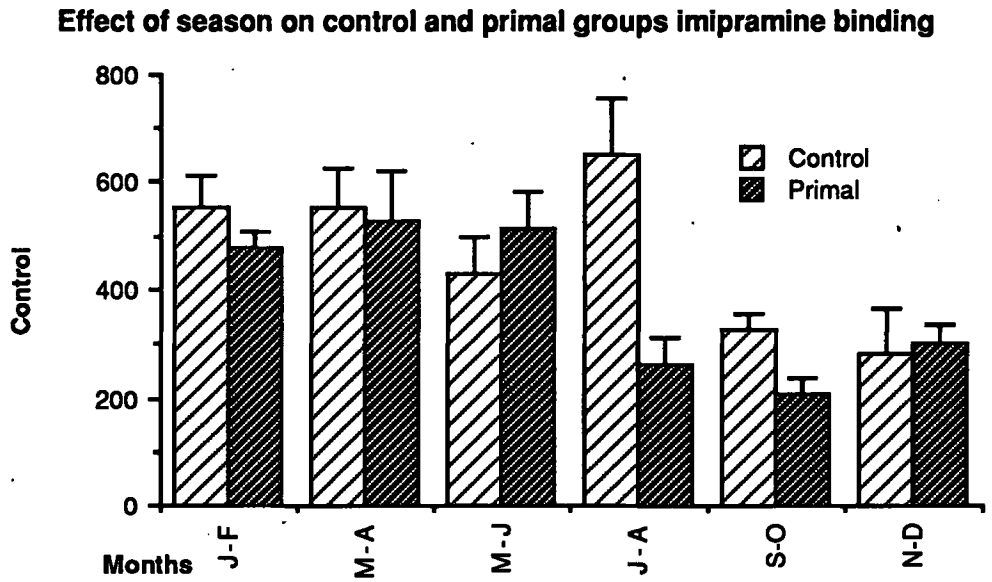


The results shown are from the Primal group only.

A very weak positive correlation is apparent

Figure 5.3

The graph below shows the effect of season on the primal and control group imipramine binding.



Control values: J-F **n=15;** M-A **n=10;** M-J **n=6;** J-A **n=8;** S-O **n=7;** N-D **n=4.**

Primal values: J-F **n=8;** M-A **n=6;** M-J **n=11;** J-A **n=10;** S-O **n=5;** N-D **n=14.**

Results are expressed as means +/- standard error of mean.

Whilst these observations were not in any way an endorsement of the theoretical claims of the particular type of psychotherapy involved, they indicated that such therapies may result in lasting biochemical changes. These data led to the current research, to investigate whether it would be possible to detect changes in biochemical binding parameters in parallel with psychological change.

Although the Primal Study provided us with some extremely interesting data it was not particularly well controlled, in as much as individual primal subjects were not matched with individual controls. Also the timing of samples, although on the same scale was different in Paris to the control samples in England. In addition the handling that samples received (transport back from Paris etc.) was potentially quite different.

Another methodological problem was that the questionnaires were not standard or well validated and were completed by therapists in France, and by the individual involved in England. For these reasons the present study was set up with highly validated self-rating questionnaires (See Chapter 6) and age and sex matched controls. It is important to emphasise that it was not a primary aim of the project to evaluate outcomes of psychotherapy as against, say, placebo or drug treatments, and I was not attempting to incorporate into the present design controls against the possibility that any observed changes in either biochemical or psychiatric rating scores may have been the result of spontaneous remission rather than the therapeutic process per se. Whilst testing the latter is an important goal of outcome studies, it must be clearly understood that the research reported in this thesis had a quite different purpose. These controls were intended to act as a population 'normal'.

CHAPTER 6

EXPERIMENTAL DESIGN

The collaborating Centre

Agreement was reached with a group of therapists working from The Open Centre (Old Street, London EC1). The Open Centre is a part of the Community Health Foundation and has been established since 1977. The Centre does not see itself so much as a clinic, but more as a growth centre, which offers a range of individual and group psychotherapies within the broad spectrum of the humanistic psychology movement (Despite the analogous name, it should be made clear that the Centre has no relation with the Open University). The range of therapies at the Centre includes; Encounter therapy, Bioenergetic therapy and Gestalt therapy. These are well-established psychotherapeutic techniques with an extensive methodological literature (e.g. Perls 1974; Lowen 1971; Wibberley 1988; Whitfield 1988; Parlett and Page 1990). Clients are carefully selected by therapists to participate in group or individual therapy and where necessary may be referred to other therapists within the group. People who are not considered appropriate for the type of therapies on offer are not taken on. All therapists at the Open Centre are highly experienced and well recognised within their field. Most clients at the Open Centre are involved in therapy at least once a week for a minimum of one hour (although generally longer). Therapists and Counsellors from the Open Centre informed new clients of the research, both verbally and in the form of a standard letter (Appendix 1), and provided the facilities required for administering the questionnaires and drawing the blood. Attempts were made to include NHS hospitals within this study, but were unsuccessful, as most centres would have patients on drug therapy in addition to the psychotherapy.

The Client sample

From January 1988, through to August 1989 new clients entering the Centre (and also clients who had been in therapy for some time but still had scope for improvement) were

invited to participate in the research. Their therapist explained the aims and procedure of the investigation to the clients as early as possible in their course of therapy. If the client was interested, he or she was given an explanatory leaflet and enabled to make contact with myself. Thereafter, the therapist was not directly involved in the research programme. Clients accepted into the research were not currently, or in the three months prior to the start of the project, regularly using psychotropic drugs, and whilst no rigorous diagnostic categories were applied, the aim was to recruit mainly those presenting clear signs of depression with or without anxiety. It was assumed that clients accepted for the study were entering a period of regular (at least weekly) one-to-one therapy or counselling or weekly group therapy in small group situations. Clients who withdrew from therapy before 3 months were discounted from the study. A total of 19 clients were included in the study, of these 12 were participating in encounter therapy, 4 in Gestalt and 3 in Bioenergetics (4 other clients were enrolled into the study but dropped out before 3 months treatment had been completed). The age range of the clients was 23-48 (mean 36) and 68% were female.

The control sample

Each client admitted into the sample was matched with a control of the same sex and similar age (age range 23-49 (mean 36) 68% female). Controls came entirely from staff at the Open University.

There is an extensive body of literature indicating that measures of serotonin function are susceptible to both circadian and circannual variation (as seen in the pilot study). Diurnal patterns of uptake of serotonin into platelets have been shown in both depressed patients and controls (Rausch *et al* 1982; Arora *et al* 1984a; Modai *et al* 1986), but they are much more variable in patients (Humphries *et al* 1985). This effect is also seen in the rat suprachiasmatic nuclei (Wirz-Justice *et al* 1983). As well as the serotonin uptake studies imipramine binding assays have indicated lower levels of binding during the night (Nankai *et al* 1986). Further evidence comes from the fact that circadian rhythms in general can be altered by psychiatric illness (e.g. Wehr and Wirz-Justice 1982) and that effective antidepressant treatment actually slows or dissociates circadian rhythms (Wirz-Justice and Campbell 1982).

Furthermore the diurnal rhythm of platelet 5-HT has actually been found to have circannual variation (Wirz-Justice and Puhringer 1978)

Circannual variation has also been extensively reported in both depressives and controls, although the period with the highest values varies from the autumn and winter (Arora *et al* 1984; Whitaker *et al* 1984) through to winter and spring (Healy *et al* 1990), and late summer and autumn (Egrise *et al* 1983; Egrise *et al* 1986; Arora and Meltzer 1988). Overall, highest values seem to be found around September.This effect has also been reported on subclasses of imipramine binding sites (DeMet *et al* 1990a). Other work however has failed to find any evidence of seasonal variation. (Galzin *et al* 1986). A study using paroxetine binding to measure circannual changes in serotonergic function found highest values in December (Klompenhouwer *et al* 1990).

The important point that is stressed by both circadian and circannual studies is that controls and subjects should be assessed at the same time of day as far as possible (certainly samples should be made at the same time of day for each individual) and at the same time of year. The effects of age and gender on both binding assays and self rated assessments are not particularly clear with various different findings reported (e.g. Klompenhouwer *et al* 1990; Maes *et al* 1988; Langer *et al* 1980; Theodorou *et al* 1989; Andersson and Marcusson 1990). The purpose of the control group was to provide a background population 'normal' value so that age, sex, circadian and circannual changes would not falsely influence the results.

The Nurses group - stressed control group

In order to provide a population of possible depressed controls co-operation was obtained from Milton Keynes General Hospital to allow recruitment of up to 30 nurses onto the study and provide the necessary facilities for blood withdrawal and administration of psychiatric rating scales.

Assessments were made on a group of 27 nurses from Milton Keynes General Hospital over a period of 1 year starting in November 1988. Every effort was made to ensure that all

nurses were sampled at each visit, however due to shift-work, holidays and sickness this was not always possible. The age range was 21-55 (mean 30) and was 89% female.

Given the uncertainty about which types of nursing are the most stressful and therefore most likely to result in depression, I chose not to specify and agreed to take nurses from anywhere in Milton Keynes General Hospital. In actual fact they came from surgical, medical and accident and emergency departments. There are a number of questionnaires designed specifically to investigate stress in the health profession (e.g. the Health Professions Stress Inventory (HPSI) Wolfgang 1988b). However the questionnaires used in this study have been successfully used in nursing studies (e.g. Motowidlo *et al* 1986; Livingstone and Livingstone 1984) and it was not our intention to try and investigate sources of stress in this population. This group was intended to act as a control group of individuals who were more likely to to be depressed than the 'normal' population but who were unlikely to receive any treatment.

The Choice of Questionnaires

The three questionnaires were all designed to give a numerical score of psychiatric rating. They were chosen after consultation with Dr Power at the Institute of Psychiatry in London as they are widely accepted questionnaires requiring no psychiatric training to administer. Each time the questionnaires were given the subject was asked to mark the descriptions which best described how they had felt over the last week. Often subjects would request help with completing the questionnaires, in these circumstances they were reminded that they should reply with how they have felt most of the time. Subjects were strongly encouraged to answer all questions, but where they were unable to the complete the whole questionnaire their results were excluded. The questionnaires chosen were three self-report questionnaires, the General Health Questionnaire 28 (GHQ-28) (Goldberg and Hillier 1979), the Beck Depression Inventory (BDI) (Beck *et al.* 1961) and the Multiple Affect Adjective Check List (MAACL) (Zuckerman and Lubin 1965)

The GHQ-28 consists of 28 multiple choice questions: it is intended to assess the general

state of well-being of the subject and breaks down into 4 "sub-scales"; somatic, anxiety, social dysfunction and depression (See Appendix 2). An overall score is given by marking all answers in the two right hand columns as one point, a score of 5 points or more (out of a possible 28) is considered to be a "psychiatric case". One problem with this questionnaire in very mild patients is that if the subject has a minor illness such as influenza the somatic score will be high and push up the overall score. For the purpose of analysis on this study figures are presented both with and without the somatic scores included. The GHQ-28 is widely recognised as a diagnostic tool particularly in epidemiological studies involving General Practitioners (e.g. Boardman 1987)

The BDI is composed of 21 multiple choice questions (see Appendix 3), each answer gives a score of between 0 and 3 points (maximum 63 points). Kendall *et al.* (1987) recommended the following cut-off scores: 0-9 = non-depressed, 10-15 = dysphoric, 16-20 = dysphoric, possibly with secondary depression, 21-30 = moderate depression, 31+ = severe depression. The BDI is very widely used in psychiatry and is acknowledged to be most useful in patients that are not too severely affected and correlates well with scores made on a Clinical Global Impression by psychiatrists (Faravelli *et al* 1986).

The MAACL is a list of 132 words (see Appendix 4), the subject is asked to mark an "X" by those words which best describe their feelings over the last few days. It is essential that this questionnaire was completed rapidly otherwise the subject may reject words simply because they appear to conflict with what they have already crossed. Of the 132 words, 43 have no scores at all associated with them, of the others some are so called "plus" words and others are "minus" words. For instance when scoring for depression words such as: awful, blue, lonely, lost, sunk, etc (plus words) score +1 point each, when marked; whereas words such as: active, alive, fine, healthy, young, etc (minus words) score +1 point each when not marked. The scoring is on three separate scales; anxiety (21 words), depression (40 words) and hostility (28 words). As this study was mainly concerned with anxiety and depression, scores are presented with and without the inclusion of hostility. Of the three scales used in this study the MAACL is the least well validated and the least frequently used.

It is worth commenting at this stage that for ease of use all of the above questionnaires are self-rated and so for this reason do not meet any rigid diagnostic or treatment effect criteria as defined by the World Health Organisation (Bech *et al* 1984). However in a recent review of questionnaires for use in the early detection of depression using questionnaires both the BDI and GHQ-28 met the designated quality criteria (Feightner and Worrall 1990).

In addition, on each of the sample dates the therapist was asked to fill in a short report containing visual analogue rating scales for anxiety and depression, and asked for any comments they may have had on the condition of the client (See Appendix 5) Unfortunately, in the event, the therapists were too busy to fill these in at the time, and it was felt that retrospective analysis was not desirable.

The Choice Of Assays

1. Measures of serotonergic function:-

As discussed in chapter 4, imipramine binding to blood platelet membranes has been used extensively as a measure of serotonergic function in the study of depressive disorder where it is found to be decreased in depressed subjects (e.g Langer and Raisman 1983; Poirier *et al* 1986; Innis *et al* 1987). The affinity of imipramine for its binding site on the platelet membrane can be altered by administration of antidepressant drugs (Rehavi *et al* 1980; Plenge and Mellerup 1985; Mellerup and Plenge 1986) and this effect has been seen to occur concomitantly in brain and platelet assays in animal studies (Briley *et al* 1982). It has also been suggested that imipramine binding may represent a possible predictor of response to antidepressant treatment (Hrdina *et al* 1985).

However a number of studies have failed to demonstrate any difference between imipramine binding in controls and depressed patients (e.g. Plenge *et al* 1988; Desmedt *et al* 1987) or an actual increase in binding in depressed patients (e.g. Mellerup *et al* 1982; Baron *et al* 1983). Some doubt has therefore been cast on the validity of imipramine as a marker for depression, and it was being investigated by the world Health Organisation (Morozov 1985) at the time when this study was being set up. The preliminary results from centres in Basle,

Brussels and Copenhagen indicated that no pronounced differences were apparent between depressed patients and matched controls (Bech *et al* 1988) and when the final results were published they confirmed the preliminary findings (Mellerup and Langer 1990). However despite extensive efforts to standardise methods across the laboratories a wide range of B_{max} values were found. The control values varied from 360 (Tokyo) to 2514 (Irvine) and the patients group from 388 (Tokyo) to 2006 (Irvine). Rihmer (1991) has suggested that these differences may be due, at least in part to latitudinal differences reflecting on day length, although it is interesting to note that those centres with shortest day length reported highest B_{max}. On closer inspection of these results it is not my opinion that they provide sufficient evidence to eliminate imipramine as a marker of depressive disorder. Whilst it is true that common diagnostic procedures were used, there still exists enormous cultural and ethnic differences in patients who will present with depression in these different countries (e.g. Moscow compared to Tokyo, Irvine, Brussels etc). This impact need not however have been as marked if the number of patients studied in each centre had been greater, the majority of centres only contributing 10-20 patients (5 in Tokyo), and in some cases significantly less controls. Whilst these results inevitably must cast some doubt over the validity of imipramine binding as a marker of depression, I feel that they are not of high enough quality for further consideration of imipramine to be discounted.

Imipramine is known to bind to at least two different sites in brain and platelets, one low affinity and one high affinity site (Conway and Brunswick 1985) and it is also recognised that the high affinity sites may exist in multiple affinity states dependent on the amount of imipramine present (Phillips and Williams 1984; DeMet and Chicz-DeMet 1990), and that different subclasses of receptors may respond differently to antidepressant treatment (DeMet *et al* 1990b). The conditions under which binding takes place could presumably influence the relative proportions of high and low affinity binding and therefore influence the results. It seems probable that quite small changes in assay methodology may account for at least part of the variation seen in results (Mellerup and Plenge 1988). Factors such as protein concentration (Arora *et al* 1985; Theodorou *et al* 1989) and the proportion of intact platelets (Friedl *et al* 1983;Svereson *et al* 1990) in the reaction mixture are all known to affect binding levels.

For these reasons an alternative to the imipramine binding assay was investigated. Measures of serotonergic metabolites in blood platelets correlate well with measures of the same metabolites in CSF (Sarrias *et al* 1990), so an alternative measure of serotonergic function was sought. Paroxetine is known to be a selective and potent inhibitor of 5-HT uptake into serotonergic neurons which binds to a single high affinity site in the brain of rats (Habert *et al* 1985). Studies in human brains have shown that paroxetine also binds to a low affinity site (Backstrom *et al* 1989) but that its high affinity binding is of higher affinity than imipramine and allows a more precise determination of B_{max} (Plenge *et al* 1990). Paroxetine is, therefore the marker of choice for investigating 5-HT uptake sites in the human (Hrdina *et al* 1989; Backstrom *et al* 1989) and animal brain (Scheffel and Hartig 1989). When the binding of paroxetine to platelet membranes is compared with imipramine it is found to have a much higher affinity (Mellerup *et al* 1983) but to show a very similar distribution within the brain (Cortes *et al* 1988). Schoemaker *et al* (1986) found that the binding of paroxetine to platelet membranes occurred with greatest affinity at 37°C and concluded that 5-HT uptake activity was better reflected by paroxetine binding at 37°C than by imipramine at 0°C.

Due to the popularity of paroxetine, particularly in brain studies of 5-HT uptake, it was decided to investigate paroxetine rather than imipramine binding to platelets. However midway through the study (when a reliable clonidine assay for α_2-adrenergic receptors had still not been achieved) an interim analysis was done on the paroxetine binding, the results of which led me to use the platelets originally assigned to the clonidine assay to do imipramine binding assays in parallel with the paroxetine. Since imipramine and paroxetine bind to different polymers within the 5-HT uptake site, it was possible that different results would be seen using the two markers (Mellerup *et al* 1985).

2. Measures of α_2-adrenergic function

As discussed briefly in the previous chapter α_2-adrenergic receptor hyperactivity has been implicated in depressive disorder (e.g. Piletz *et al* 1990). However very variable results have been reported using radioligand binding studies to platelets. Yohimbine is a potent α_2 antagonist (Garcia-Sevilla *et al* 1981; Motulsky and Insel 1981; Motulsky *et al* 1980) and so if used in platelet binding studies an increased binding would be predicted in depressed patients. In actual fact no difference between depressed patients and controls is seen (e.g. Daiguji *et al* 1981; Stahl *et al* 1983). Rauwolscine is also a highly selective α_2-antagonist and also shows no difference in platelet binding studies between depressed patients and controls (e.g. Pimoule *et al* 1983).

Clonidine is an α_2 mixed agonist-antagonist which, like rauwolscine and yohimbine is highly specific (Garcia-Sevilla *et al* 1981; Shattil *et al* 1981). It has been shown that the long-term administration of amitriptyline decreases the number of high affinity sites in neural membranes isolated from specific areas of the rat brain (Smith *et al* 1981). Studies investigating binding of clonidine to platelet membranes of depressed patients have found increased numbers of binding sites although no change in affinity (Pandey *et al* 1989; Garcia-Sevilla 1981). Similar results are also seen with the closely related compound para-aminoclonidine (Piletz *et al* 1990). This is in keeping with the adrenergic theory of depression indicating greater numbers of activated α_2-adrenergic receptors and so the clonidine assay was originally chosen for the analyses. However, failure to produce a reliable assay with the quantities of platelets available led to utilision of the imipramine assay of 5-HT uptake sites rather than the clonidine assay.

Investigation procedure

On entering the sample, clients, controls and nurses were asked to complete the three self-report questionnaires, the GHQ-28, MAACL and the BDI. At the same time a blood sample was drawn for preparation of platelets. The same protocol was repeated on five subsequent occasions: 1 month, 2 months, 3 months, 6 months and 12 months after the start of therapy (even if the client dropped out of therapy after three months or so, efforts were

made to retain him or her in the sample). As far as possible, sampling from the controls was done at the same time as from the clients, and sampling for any one individual was carried out at the same time of day on all occasions. In general, questionnaires were administered and blood samples taken at the psychotherapy centre (for clients), but on occasion and where appropriate the site was changed for mutual convenience of client and researcher. Sampling from controls was conducted at the Open University Medical Centre. Sampling from the nurses was completely independent from the control sampling times and took place at Milton Keynes General Hospital, but as far as possible individual nurses were sampled at the same time of day. All questionnaires and blood samples were coded as they were taken so as to preserve confidentiality. These were then independently recoded to ensure that subsequent analyses were performed blind.

The Assay Procedures

For the platelets, venous blood (20ml) was drawn into tubes containing citric acid/sodium citrate/dextrose anti-coagulant and transported to the Brain Research Group laboratories at the Open University. Appropriate precautions were taken in the drawing of blood in the light of general medical good practice and the present concern over the hazards of HIV and hepatitis infection.

Platelets were prepared according to the method of Stahl *et al* (1977) as follows:- the blood was centrifuged at 600g for 10 minutes at room temperature and the platelet-rich plasma removed; the remaining blood was spun again to ensure that as much as possible of the plasma was collected. The platelet-rich plasma was then divided into two tubes, one containing approximately a third of the sample and the other the remaining two thirds; both tubes were then spun at 18000g for 10 minutes at 4^{o}C. The smaller sample was used for the paroxetine assay and the larger one was intended to be for the clonidine assay, but as no reliable assay was found this fraction was used for an imipramine binding assay.

Preparation of platelet membranes for paroxetine binding assay:

Platelet membranes were prepared using the method described by Phillips *et al.* (1984). The

platelet pellet was resuspended in 2ml cold 50mM Tris HCl buffer containing 120mM NaCl and 5mM KCl (pH 7.5), centrifuged again, resuspended in 1ml of the same buffer and stored frozen at -20°C until it was assayed. (It is well established that platelet preparations may be stored for several months in this way without loss of imipramine binding activity, e.g. Lewis and McChesney (1985a)) For the assay, platelet pellets were disrupted using a homogeniser (20 strokes) and spun at 39000g for 10 minutes, at 4°C. The pellet was resuspended in 1ml of buffer and sonicated, the membrane fraction was then divided into the appropriate aliquots.

Preparation of platelet membranes for clonidine binding assay (used for the imipramine binding):

Platelet membranes were originally prepared for use in the clonidine binding assay using a slightly modified version of the method described by Shattil *et al.* (1981). The platelet pellet was resuspended in 2ml of ice cold buffer containing 50mM Tris HCl, 100mM NaCl, 5mM EDTA (pH7.4), centrifuged at 1800g for 10 minutes at 4°C, then resuspended in 2ml of the same buffer and stored frozen at -20°C. (As the clonidine assay was not actually used, these samples were used for the imipramine binding assay and after thawing were washed in paroxetine buffer twice to remove EDTA then homogenised and sonicated as above.) It was very important that the process of sonication and homogenisation was done accurately and in a repeatable manner as the proportion of intact platelets can have a marked effect on results (Friedl *et al* 1983).

For the samples used to try to develop the clonidine assay the suspension was thawed and spun again as before. The washed platelets were then resuspended in a hypotonic buffer containing 5mM Tris HCl, 5mM EDTA (pH 7.5) and homogenised as described above. This suspension was then centrifuged at 3900g for 10 minutes at 4°C and the pellet resuspended in the same buffer and centrifuged a second time. The resultant pellet was then resuspended in 1.5ml of a buffer containing 70mM Tris HCl, 0.5mM EDTA, 8mM $MgCl_2$, 0.8mM sodium ascorbate.

Protein concentration of all membrane suspensions was determined on a portion of the

preparation using a modified version of the method of Lowry *et al.* (1951). 10µl of platelet membrane suspension was added to 3ml of alkaline carbonate and the volume made up to 5ml with distilled water. Similar tubes were set up with either no protein (blank), or a known amount of bovine serum albumin (Protein standard). The tubes were left to stand at room temperature for 10 minutes, then incubated with 0.3ml of Folin's reagent for 30 minutes at room temperature. The depth of colour produced was then read on a spectrophotometer at 500nM.

For the paroxetine binding assay approximately 0.1-0.2 mg of platelet membrane was incubated for 3 hours at 37°C in Tris buffer as above containing approximately 9nM of ^{3}H-paroxetine in the presence or absence of 1mM serotonin. These conditions were chosen on the basis of previous experience and data presented in the following chapter, to give maximal binding, they are very similar to the method described by Schoemaker *et al* (1986). I did not explore possible changes in affinity of the receptor, because this has not been reported as showing changes in the context of psychic distress or drug treatment. Following incubation, the mixture was diluted with 3ml ice-cold buffer and filtered under vacuum through Whatman GF/F glass fibre discs. The discs were washed three times with 3ml of buffer, dried overnight at 4°C and bound radioactivity measured in a scintillation counter. All assays were in sextuplicate (three with, three without, serotonin). Specific binding activity was taken as the difference between radioactivity bound in the presence and absence of serotonin and expressed as fmol. paroxetine bound per mg protein. An identical procedure was followed for the imipramine binding assay except that samples were incubated on ice for 1hour 15 minutes and specific binding was determined using 1.2mM 5-HT.

The methodology for the clonidine assay would have been similar to the paroxetine assay but it proved impossible within the timescale of this research to obtain good repeatable results. This is discussed in more detail later.

Statistical analyses

As discussed earlier the purpose of the control group was to act as a population 'normal' and clients and controls although matched for age and sex were not paired in any other way. Nurses were compared to the same control group as the clients and no attempt was made to match them in any way. For this reason mean values for the control group were taken to represent the population and the clients and nurses values were compared to this using a one tailed t-test. Change over the 12 month period for for each parameter analysed was assessed using a paired t-test to compare the value obtained at baseline with the final (12 month value). Additionally analysis of variance (ANOVA) and repeated measures ANOVA were performed to assess the change in the parameters over time.

Some researchers (e.g. Maes et al 1988) have reported differences in male and female reporting on self report questionnaires. For this reason male and female data were analysed separately in addition to the general analysis to see if there were any obvious differences.

The General Health Questionnaire and the Multiple Affect Adjective Checklist both break down into separate components, some sub-analyses of these scales were also made.

HYPOTHESES

On the basis of the information discussed in the previous chapters concerning serotonergic and adrenergic function in depression my hypotheses were:-

a) that the average levels of imipramine and or paroxetine binding to platelets derived from the blood of depressed people entering psychotherapy would be significantly lower than that of the matched control group.

b) that during the course of a period of psychotherapy of up to a year, average levels of imipramine and, or paroxetine binding in the client sample would rise towards those of the control group.

c) that for any individual client, changes in imipramine/paroxetine binding levels during the course of treatment would show correlations with changes in psychic state as measured

using standard psychiatric rating scales.

d) that those nurses whose questionnaires indicate signs of depression/anxiety would show altered platelet imipramine and paroxetine binding levels, and that any improvement in their psychiatric rating would correlate with their binding levels moving towards those of control values.

e) that the average levels of clonidine binding to platelets derived from the blood of depressed people entering psychotherapy would be significantly higher than that of the matched control group.

f) that during the course of a period of psychotherapy of up to a year average levels of clonidine binding in the client sample will fall towards those of the control group.

g) that for any individual client, changes in clonidine binding levels during the course of treatment will show correlations with changes in psychic state as measured using standard psychiatric rating scales.

h) that those nurses whose questionnaires indicate signs of depression/anxiety will show altered platelet clonidine binding levels, and that any improvement in their psychiatric rating will correlate with their binding levels moving towards those of control values.

CHAPTER 7

DEVELOPMENT OF THE ASSAYS

Imipramine binding assay

This assay had previously been worked on in this laboratory. Due to the failure to get the clonidine assay to work (as discussed later) it was decided to use imipramine and see whether any differences would be apparent between imipramine and paroxetine binding. As this method had already been used in the laboratory confirmation of the methodology was relatively straightforward. Freezing is known to not markedly effect imipramine binding, and this was confirmed by assaying freshly prepared platelets compared with samples frozen for 4 months.

The effect of increasing amounts of protein from 0.01mg to 0.2mg was assessed, higher amounts of protein were not investigated as they were unlikely to be available. There was no noticeable effect of the amount of protein on specific binding per mg of protein. As protein concentration increased, binding increased in a linear manner (see fig 7.1).

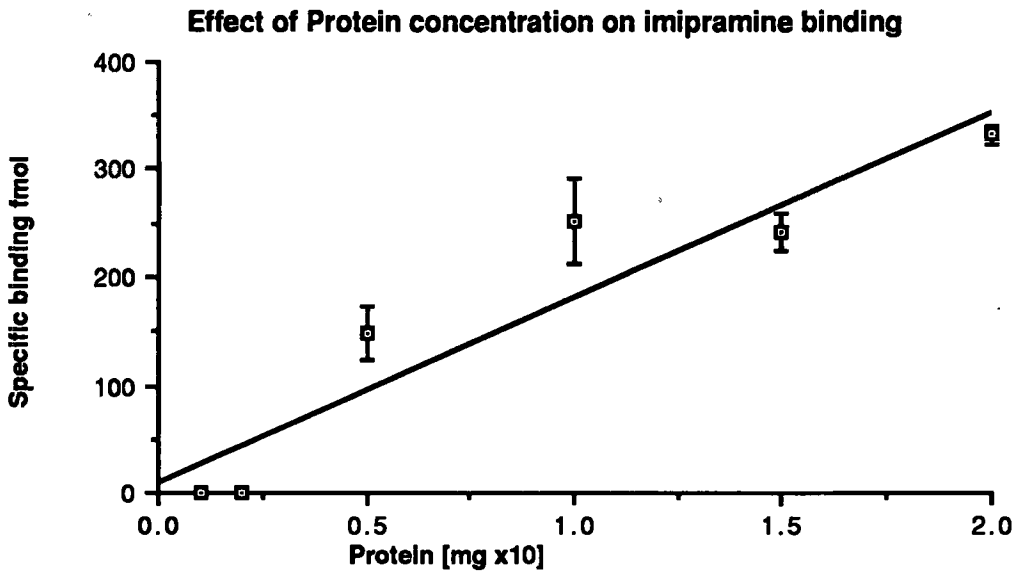
The effect of imipramine concentration on specific binding was assessed using concentrations of 0 to17nM of imipramine. The optimal concentration was found to be 8.6nM achieving approximately 85% specific binding (See figure 7.2). The B_{max} for imipramine binding was estimated at 575 fmol/mg protein, which is at the lower end of the range found in previous studies (e.g WHO multicentre collaborative study (Mellerup and Langer 1990))

Additionally the concentration of 5-HT required for maximal inhibition of specific binding was ascertained using concentrations of 5-HT from 0mM to 2mM. Maximal inhibition appeared to be achieved at around 1mM., but it was felt that it was preferable to increase this slightly to 1.2mM to ensure that all specific binding would be detected (see fig 7.3).

The effect of time on imipramine binding up to 90 minutes was assessed. The graph shows that no binding was apparent at either 20 minutes or 40 minutes, the reason for this is not clear but may be due to the fact that the reaction takes place on ice and may be very slow to get started. In previous imipramine binding assays the incubation time had been 1 hour on ice, in view of the data shown in figure 7.4 this was extended to 1 hour 15 minutes

Figure 7.1

The graph below indicates that increasing the protein concentration in the reaction mixture up to 0.2mg does not markedly effect the specific binding of imipramine per mg of protein.



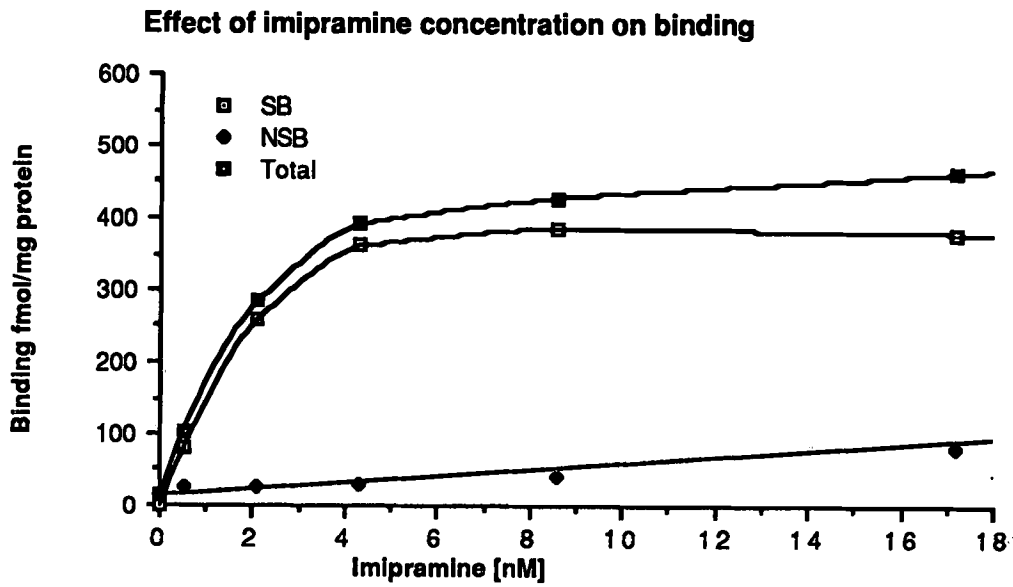
The results reported on this graph come from several experiments (**0.01mg** n=1 **0.02mg** n=1; **0.05mg** n=4; **0.10mg** n=5; **0.15mg** n=6; **0.20mg** n=6). All assays were performed in triplicate (Intra-triplicate variation 3-6%). The results are expressed as means +/- standard error of mean.

All assays were incubated for 1 hour and 15 minutes at 0^0C (on ice) with 8.6nM of imipramine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 1.2mM 5-HT and is expressed in terms of disintegrations per minute.

Figure 7.2a

The graph below shows the effect of increasing the imipramine concentration on binding. It indicates an optimal imipramine concentration of around 9nM.



SB=Specific binding, NSB=Non-specific binding, Total=Total Binding

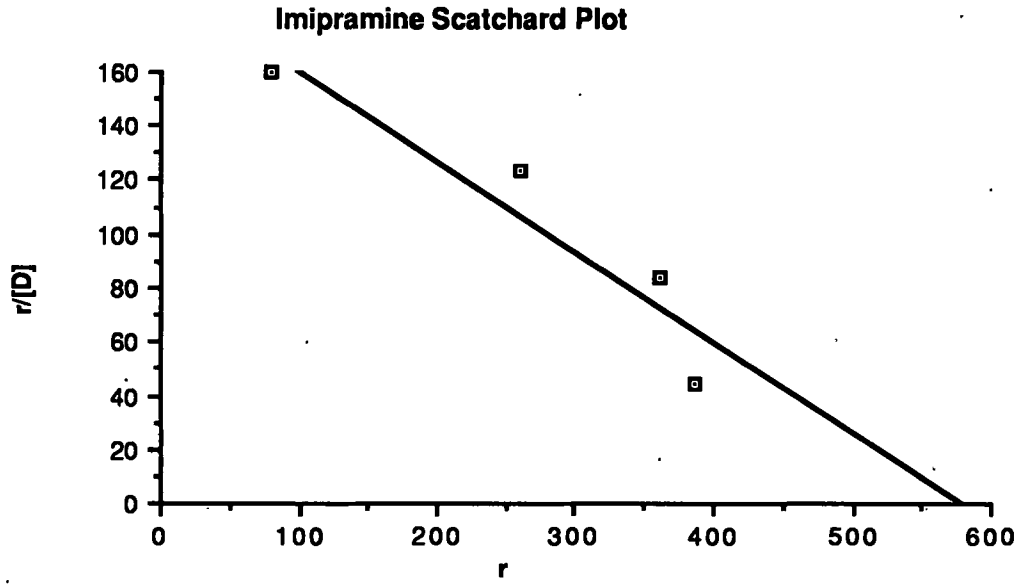
The results reported on these graphs come from more than one experiment (n=1 for all points). All assays were performed in triplicate (Intra-triplicate variation 3-7%). The results are expressed as means +/- standard error of mean.

All assays were incubated for 1 hour and 15 minutes at 0^0C (on ice) . After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 1.2mM 5-HT and is expressed in terms of disintegrations per minute.

Figure 7.2b

A Scatchard analysis was performed using the first 4 points of the saturation curve for specific binding

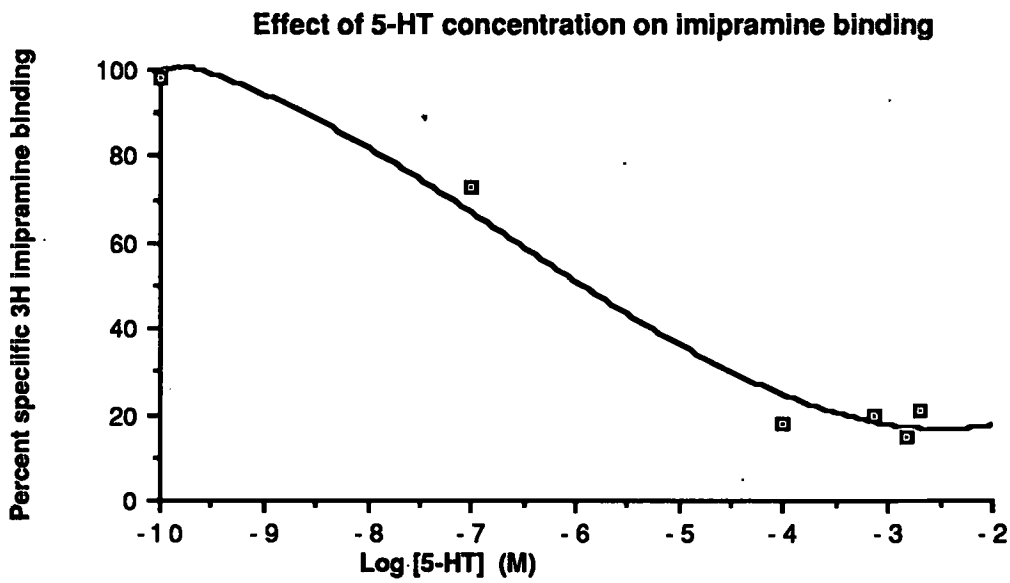


r = fmol imipramine bound/ mg protein

[D] = free imipramine (nM)

Figure 7.3

The graph below shows the effect of increasing 5-HT on specific binding of imipramine. These data indicated that approximately 1.2mM 5-HT is an optimum amount for determining specific binding.



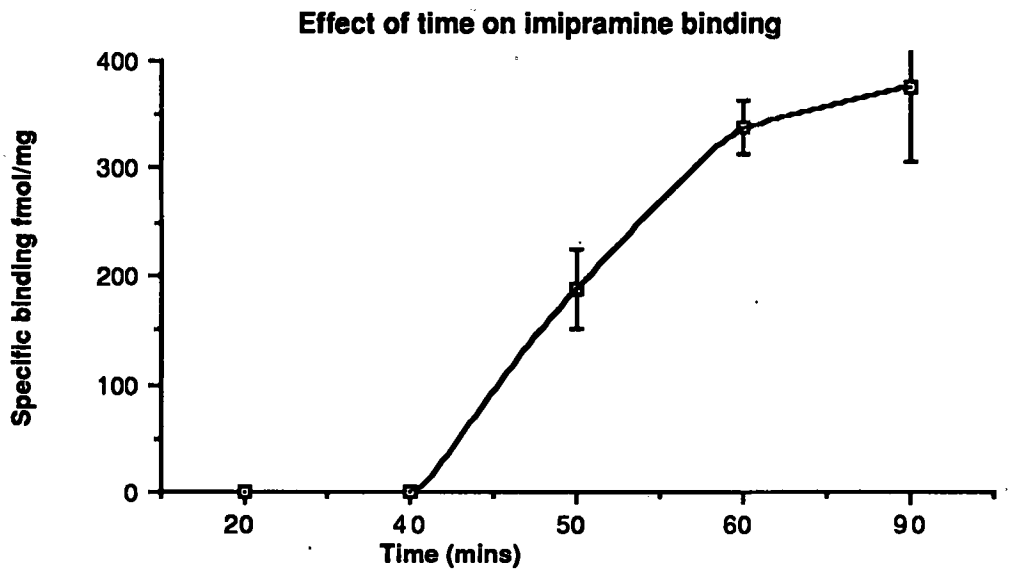
The results reported on this graph come from more than one experiment (n=1 for all points). All assays were performed in triplicate (Intra triplicate variation was 3-5%)

All assays were incubated for 1 hour and 15 minutes at 0^0C (on ice) with 8.6nM of imipramine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding is expressed in terms of disintegrations per minute per mg of protein.

Figure 7.4

The graph below shows the effect of time on specific binding of imipramine and indicates that 1 hour and 15 minutes is sufficient time to obtain maximum binding.



The results reported on this graph come from one experiment (**20 mins** n=3; **40 mins** n=3; **50 mins** n=2; **60 mins** n=3; **90 mins** n=3). All assays were performed in triplicate (Intra-triplicate variation was 4-6%). The results are expressed as means +/- standard error of mean.

All assays were incubated at 0^0C (on ice) with 8.6nM of imipramine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 1.2mM 5-HT and is expressed in terms of disintegrations per minute per mg of protein.

Paroxetine binding assay

The method was to some extent established from work previously performed in this laboratory on imipramine binding. The assay was therefore based on this technique but was conducted at a higher temperature and needed some modification. Preliminary work indicated that an incubation time of three hours was most appropriate so this was used throughout. The effect of freezing was determined by assaying freshly prepared platelet samples and ones stored frozen for 3 months. There was no apparent effect on specific binding.

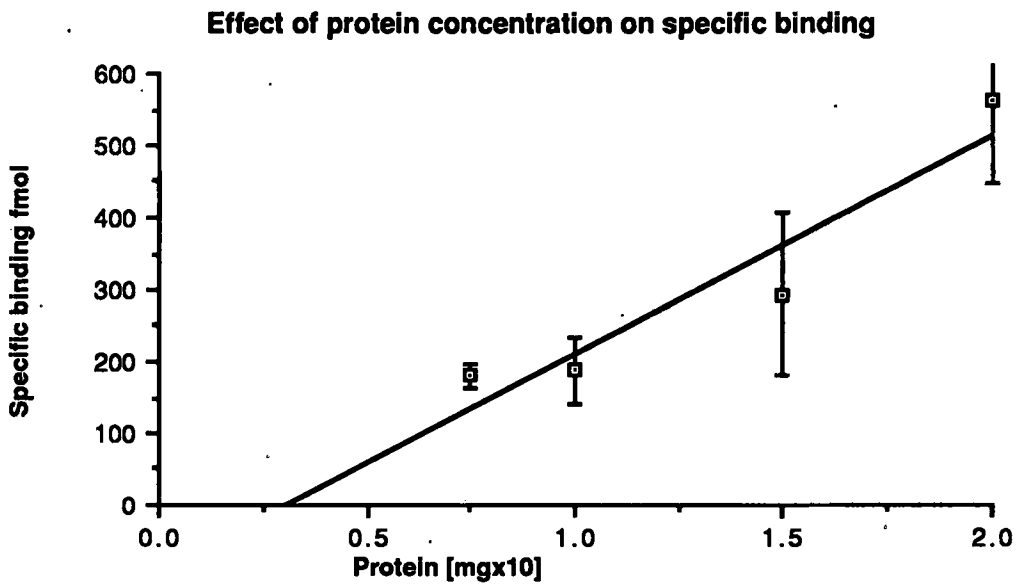
Previous studies have shown that protein concentration can have a marked effect on the apparent binding per mg of protein (Arora *et al* 1985; Theodorou *et al* 1988). In order to ensure that this would not effect the results, specific binding was determined using varying concentrations of protein up to 0.2mg. (Concentrations of more than 0.2mg were not likely to be available for assay). The results of these assays indicated that there was not likely to be major effect on the specific binding in terms of paroxetine bound/mg of protein (see Fig 7.5).

The optimal concentration of paroxetine was assessed by a series of assays using concentrations of 0 to 26nM of paroxetine, the highest percentage specific binding being realised at 9 nM(approx 70%). As a result a concentration of 9nM was chosen for the assays (see fig 7.6) The B_{max} obtained from these data was 520 fmol/mg protein which is similar to those reported in the literature (e.g.D'haenen *et al* 1988)

In order to determine the minimum effective concentration of 5-HT required to inhibit specific binding of paroxetine, a series of assays were performed using concentrations of 5-HT from 0 to 1.2mM. The minimum effective concentration for maximum inhibition of specific binding appeared to be 1mM (see Fig 7.7).

Figure 7.5

The graph below indicates that increasing the protein concentration in the reaction mixture up to 0.2mg does not markedly effect the specific binding of paroxetine per mg of protein.



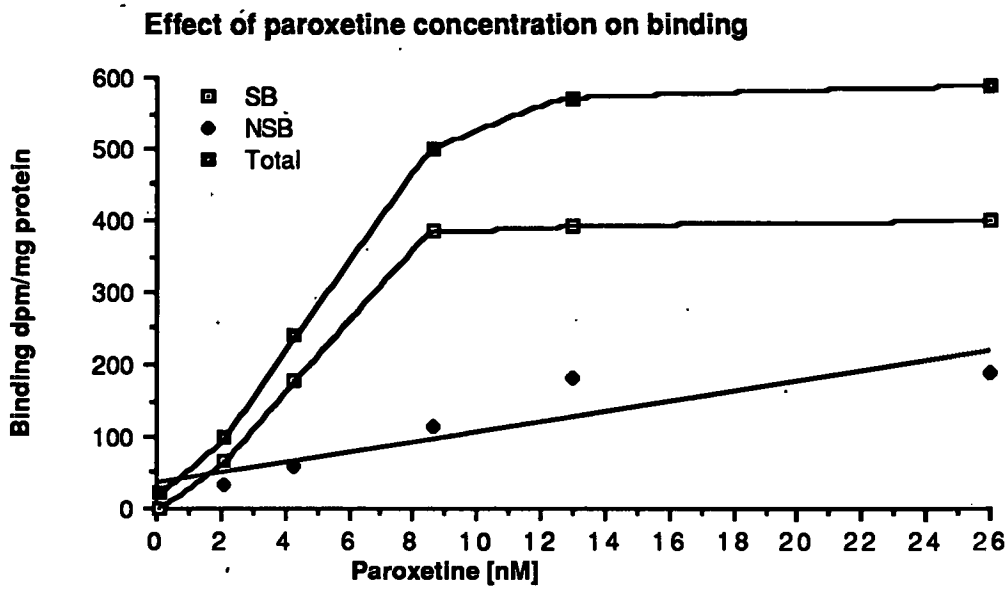
The results reported on this graph come from several experiments (**0.05mg** n=3; **0.10mg** n=3; **0.15mg** n=5; **0.20mg** n=6). All assays were performed in triplicate (intra-triplicate variation 3-5%). The results are expressed as means +/- standard error of mean.

All assays were incubated for three hours at 37^0C with 8.6nM of paroxetine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 1mM 5-HT and is expressed in terms of disintegrations per minute.

Figure 7.6

The graph below shows the effect of increasing the paroxetine concentration on binding. It indicates an optimal paroxetine concentration of around 9nM.



SB=Specific binding, NSB=Non-specific binding, Total=Total Binding

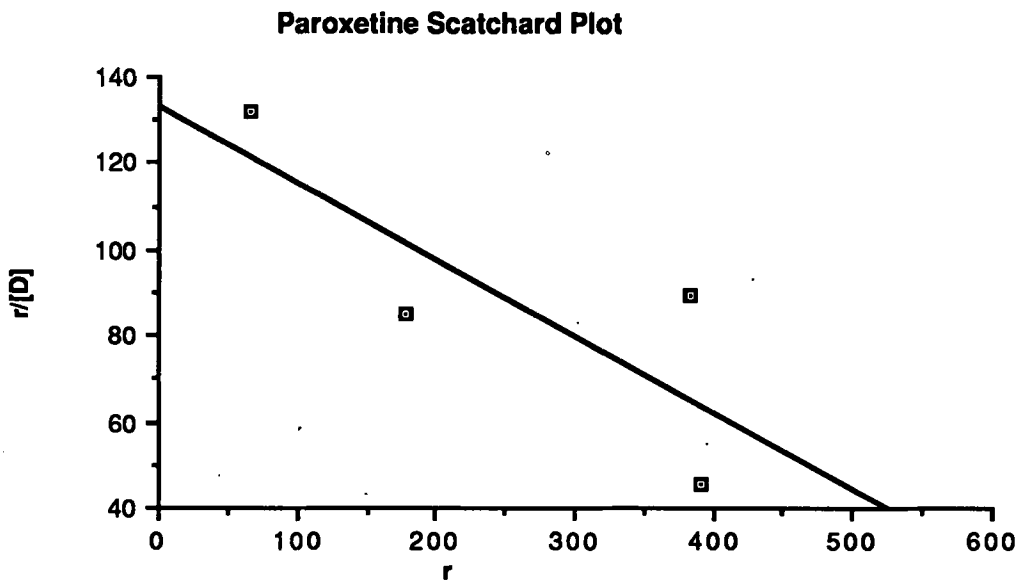
All assays were performed in triplicate (Intra-triplicate variation was 5-8%)

All assays utilised approximately 0.2 mg of protein and were incubated for three hours at 37^0C. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 1mM 5-HT and is expressed in terms of disintegrations per minute per mg of protein.

Figure 7.6b

The Scatchard analysis was performed using the first 4 points of the specific binding saturation curve.

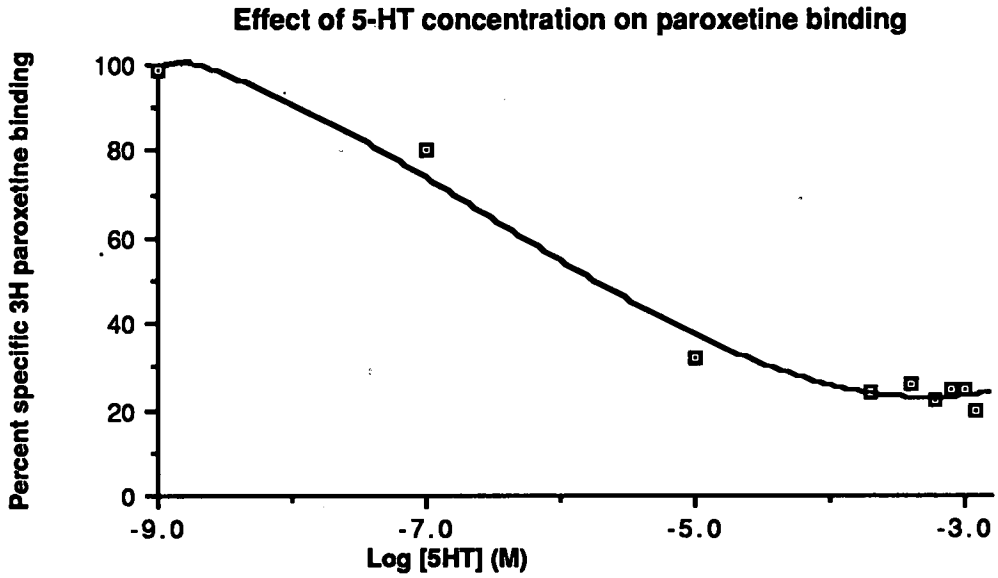


r = fmol paroxetine bound/ mg protein

[D] = free paroxetine (nM)

Figure 7.7

The graph below shows the effect of increasing 5-HT concentration. The data indicate that approximately 1mM 5-HT is the ideal concentration.



The results reported on this graph are from more than one experiment. All assays were performed in triplicate (Intra-triplicate variation 3-8%)

All assays utilised approximately 0.2mg of protein and were incubated for three hours at 37^0C with 8.6nM of paroxetine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Clonidine binding assay

The methodology for this assay caused considerable problems. Initial attempts could not demonstrate any specific binding in the size of samples used. Previous work has generally used much larger quantities of blood (e.g.Cameron *et al.* 1984) but work on small samples has been successfully conducted in the past (Shattil *et al* 1981). Some small improvements were made to the method as detailed below, but the main problem encountered was the failure to reproduce results.

Slight increases in specific binding (~5%) were found when the temperature was raised from 25 to 37°C. Although this was only a small improvement it was decided to run future assays at 37°C.

When filter binding was measured (by filtering the label without any protein present) it was found to be extremely significant - in some cases equal to the non-specific binding. Different filters were tested (Whatman GF/B,GF/C and GF/F) and Whatman GF/F were found to have the lowest filter binding. However it still accounted for at least 80% of the non-specific binding.

Previous workers (e.g. Cameron et al 1984) had used an incubation time of 30 minutes. Binding assays were conducted at times from 10 minutes to 90 minutes and these findings agreed with a minimum time of 30 minutes for the assay (see fig 7.7).

The effect of using different concentrations of clonidine ranging from 5nM to 30nM was assessed and a concentration of about 20nM was found to be sufficient to achieve maximal binding (see Fig 7.8). However this result was only found in one experiment and proved impossible to repeat. Other attempts to find an optimal concentration did not produce any consistent pattern of results.

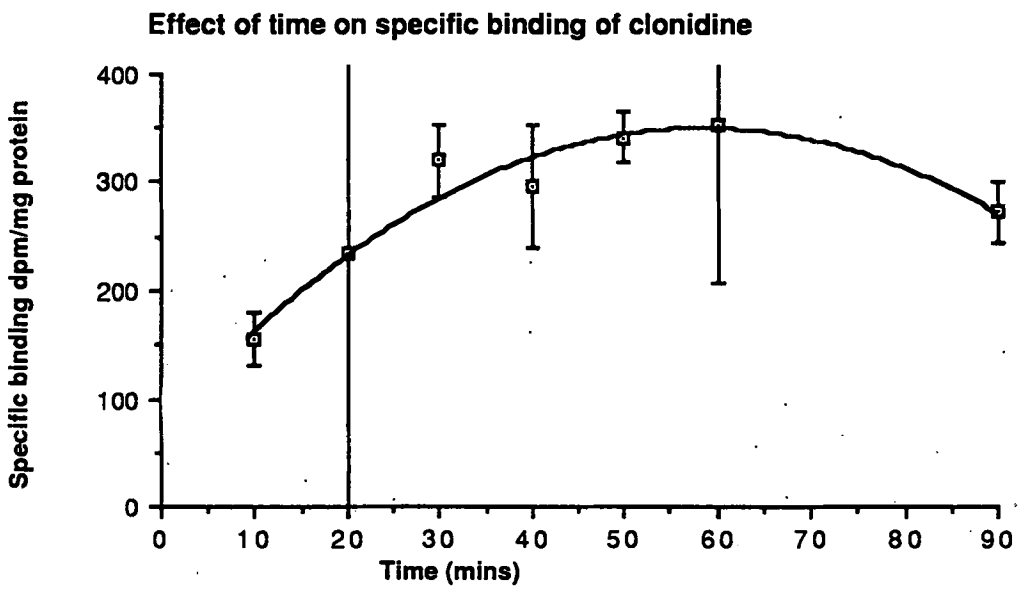
The principal problem encountered in trying to improve the assay was a failure to repeat results. Possible reasons for this, such as fluctuations in the temperature of the assay, slight

variations in the buffer etc. were all discounted. The most probable cause of the variation seemed to be the length of time for which the platelet membrane sample was frozen. In order to investigate this samples were frozen for periods of one day to two weeks and the effect of phentolamine concentrations on binding determined after the different lengths of freezing. The results which are illustrated in figure 7.9 indicated that there might be some loss of specificity as the sample was frozen for longer. However, although day 1 showed the highest specific binding and day 14 the lowest day 7 and day 8 were very different. Furthermore if 14 days freezing was having the dramatic effect seen on the 14 day sample then this assay would not have been suitable for my purposes.

In order to investigate the effects of longer term freezing, samples were frozen for periods of one week through to ten weeks and specific binding determined using a constant concentration of phentolamine at 120mM. These results further confounded the picture by indicating that the longer the sample was frozen the greater the specific binding (see fig 7.10).

Figure 7.8

The graph below shows the effect of time on clonidine binding, it indicates that around 30 minutes would be sufficient to achieve maximal binding.



The results reported on this graph came from two experiments (**10mins** n=3; **20mins** n=3; **30mins** n=5; **40mins** n=3; **50mins** n=3; **60mins** n=2; **90mins** n=3). The results are expressed as means +/- standard error of mean.

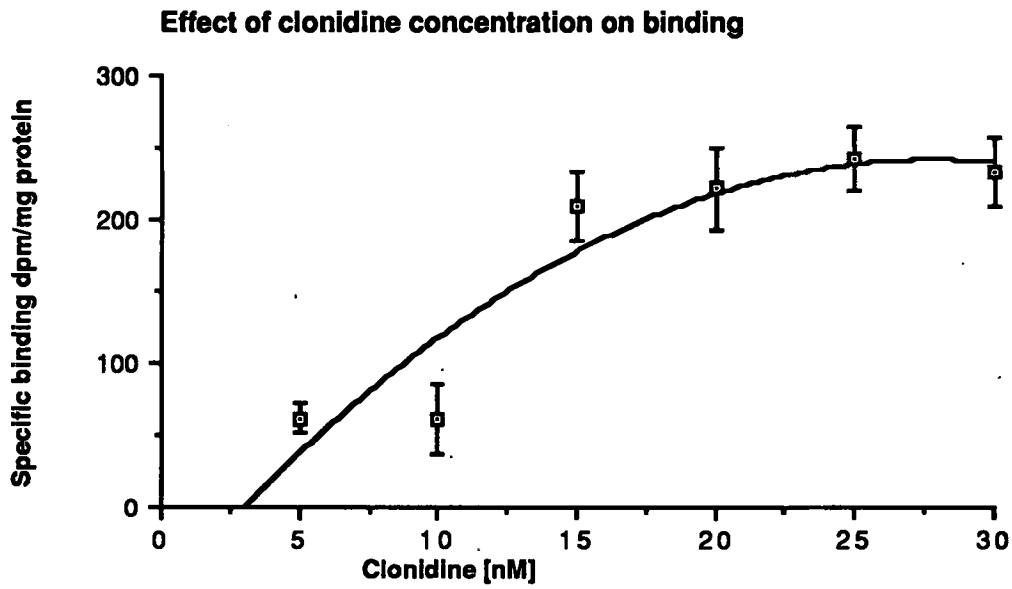
All assays utilised approximately 0.2mg of protein and were incubated at 37^0C with 20nM of clonidine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 120mM phentolamine and is expressed in terms of disintegrations per minute per mg of protein.

(All values were corrected for filter binding)

Figure 7.9

The graph below shows the effect of increasing the clonidine concentration, on binding. It indicates an optimal clonidine concentration of around 20nM.



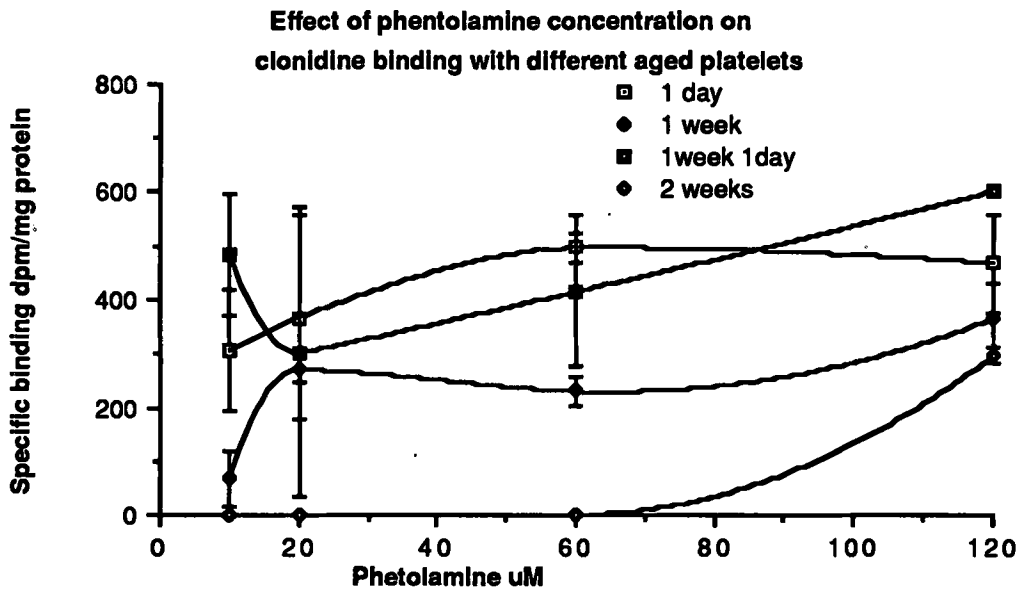
The results reported on this graph were from one experiment (n=3 for all points). The results are expressed as means +/- standard error of mean.

All assays utilised approximately 0.2mg of protein and were incubated for 30 minutes at 37^0C. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 120mM phentolamine and is expressed in terms of disintegrations per minute per mg of protein.
(All values were corrected for filter binding).

Figure 7.10

The graph below shows the effect of increasing phentolamine concentration with different ages of platelet samples. It indicates that there may be an effect of age on the specific binding of clonidine.



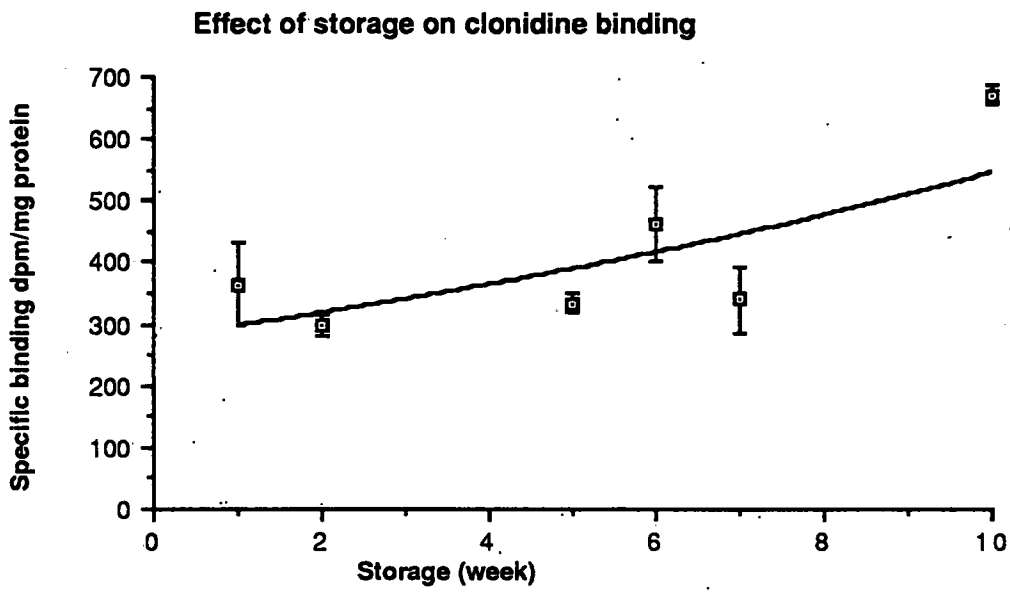
The results expressed on this graph come from four experiments (1 day old samples; 1 week old samples; 1 week and 1 day old samples; 2 week old samples). n=3 for all points. The results are expressed as means +/- standard error of mean.

All assays utilised approximately 0.2mg of protein and were incubated at 37^0C with 20nM of clonidine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding is expressed in terms of disintegrations per minute per mg of protein. (All values were corrected for filter binding)

Figure 7.11

The graph below the effect of storing platelet samples on specific binding of clonidine. The graph seems to indicate that the longer the sample is stored the greater the specific binding.



The results reported on this graph come from a single experiment (n=3 for all points). The results are expressed as means +/- standard error of mean.

All assays utilised approximately 0.2mg of protein and were incubated at 37^0C with 20nM of clonidine. After incubation they were filtered through Whatman GF/F filters and washed three times with ice cold buffer.

Specific binding was determined by inhibition with 120mM phentolamine and is expressed in terms of disintegrations per minute per mg of protein.
(All values were corrected for filter binding)

CHAPTER 8

RESULTS FROM THE PSYCHOTHERAPY AND CONTROL GROUPS

The results presented in this chapter are from the psychotherapy clients and controls. Data are compared in terms of imipramine and paroxetine binding values as well as questionnaire scores. Additionally an evaluation of the seasonality of the data and possible gender differences are made.

There were no significant differences between the groups with respect to age or gender as shown in table 8.1. (This was, however planned by the age and gender matching of the subjects in the trial.). The choice of controls is discussed fully in Chapter 6, however all controls were staff from the Open University and were intended to act as a 'population normal'. I did not chose to use untreated depressed patients or placebo tablet patients as the aim of the study was not to prove efficacy of psychotherapy.

Table 8.1. Age and gender of subjects.

	Clients (N=19)	Controls (N=19)
Age: Mean	36	36
Range	23-48	23-49
Sex: % female	68	68

Changes seen in the questionnaire scores

Beck Depression Inventory (BDI)

Client values at the start of the study and up to the end of the first three months were significantly higher than control values ($P<0.05$ at 0 and 1 month and $P<0.01$ at 2 and 3 months). After 6 months of therapy, BDI scores for clients were only slightly higher than controls and continued to fall up to 12 months, where the difference in client and control values was very small (less than 1 point). See figure 8.1.

As with all of the questionnaires used in this study, the higher the score the greater the level of psychiatric disorder. According to Kendall *et al*'s (1987) criteria, a score of 10 or more indicates dysphoria although not depression. Client scores started with an average of 9.6 (+/- 1.4) indicating a mild level of affective disorder equivalent, in general terms, to low mood.

Comparison of baseline data (0 month) with the 12 month data using student t-test did not reveal any significant change for the control values, but there was a significant change in client values ($p<0.05$). ANOVA and repeated measures ANOVA failed to demonstrate a significant difference in client and control values over time.

Sex related differences in the reporting of self rated questionnaires have been observed by some workers (e.g. Maes *et al* 1988), so for all data separate assessments have been made on male and female results to see if there were any marked differences. When male results were analysed separately the differences in the client and control values became more extreme and were still apparent at the end of treatment (see fig 8.2). However this appears to be due mainly to the fact that the control males scores were lower than control females rather than the client males scoring higher than client females. When female BDI data were analysed separately, the differences in the scores for client and control data did not reach statistical significance (possibly due to small sample size), but a very similar pattern of results was seen as with the entire data set (see fig 8.3). Therefore it was concluded that

there was no marked gender difference on this scale for the client subjects but that amongst the control population females appeared to score higher than males, although this did not reach statistical significance.

General Health Questionnaire (GHQ-28)

The GHQ-28 values from clients were higher than controls during the first three months of the study (statistically significant at 1,2 and 3 months $P<0.05$). As therapy continued the values fell to around the same as the controls, as shown in Fig 8.4. As defined in chapter 6 a person is considered as a 'psychiatric case' if they score 5 or more on the GHQ-28 (Goldberg and Hillier 1979). For the first 3 months of the study the client group averaged scores of 5.9 (+/-1.4) to 7.1 (+/-1.6), indicating that although no rigid diagnostic criteria had been applied I did actually have a group suffering from a small but significant level of psychiatric disorder. The control group averaged 2.5 (+/-1.2) to 3.4 (+/-1.5) over the entire period of the study, and the client levels eventually fell to 3.0 (+/-1.4) by the 12 month sample.

A comparison of the first and last assessments for client and control values (0 months vs 12 months) using a Students t-test, did not reveal any significant changes over time, ANOVA and repeated measures ANOVA also failed to demonstrate any statistically significant differences in client and control scores over time. Separate analysis of male data revealed a similar pattern of results as with the combined data ($P<0.05$ at 1 month) , however as with the BDI scores male control values were lower than the female data (see fig 8.5). When female data were analysed separately the same pattern of results was seen (see Fig 8.6) but the only time point where the differences were actually significant was at 2 months ($P<0.05$). Given however, that the separated male and female data sets followed broadly the same pattern of results as the combined male and female data it was concluded that there were no major gender differences, although as with the BDI control females did appear to score higher than control males.

The GHQ-28 depends for 25% of its score on somatic symptoms. When comparing a

group of moderate or severe depressives with controls the influence of the somatic score is not likely to heavily bias the results if a few people suffer from a minor illness such as colds and flu. However owing to the fact that the clients had a relatively mild depressive illness, the influence of somatic symptoms could be quite great so they were removed to see if this would affect the results (see fig 8.7). Somatic symptoms represent 6 out of the 28 questions, so a psychiatric case would now be one with 3.75 points. It was found that client values were in the range 4.2 (+/-1.1) to 4.7 (+/-1.4) for the first 3 months and then fell to the same level as control values. Removal of somatic symptoms did not markedly affect the significance of the results except that the baseline value (0 months) also reached significance (0,1,2 and 3 months $P< 0.05$).

Student t-tests comparing the GHQ without somatic symptoms at the first and last visit (0 month vs 12 month) approached a significant difference for the client values ($P=0.107$).

Multiple Affect Adjective Checklist (MAACL)

As with both the BDI scores and the GHQ-28 scores, significant differences were found between client and control values during the first 3 months of the study. These differences were highly significant at the start of the study (0,1,2 and 3 months $P<0.01$), but unlike the BDI and the GHQ the differences remained over the duration of the research period (6 and 12 months $P<0.05$) (see fig 8.8). What makes this even more complicated to account for is the fact that client values did not fall towards those of control values; rather that control values rose towards the clients. ANOVA and repeated measures ANOVA did not reveal any statistically significant differences between client and control values over the course of the study.

When the male and female data were analysed separately significant differences were found up to the end of the first three months (Male; 0 and 1 month $P<0.01$, 3 months $P<0.05$: Female; 0 and 1 month $P<0.05$, 2 and 3 months $P<0.01$) but not at six or twelve months. However on both graphs the pattern of results was the same as the combined graph

indicating that there were no significant gender differences in the way the questionnaire was answered (see figs 8.9 and 8.10).

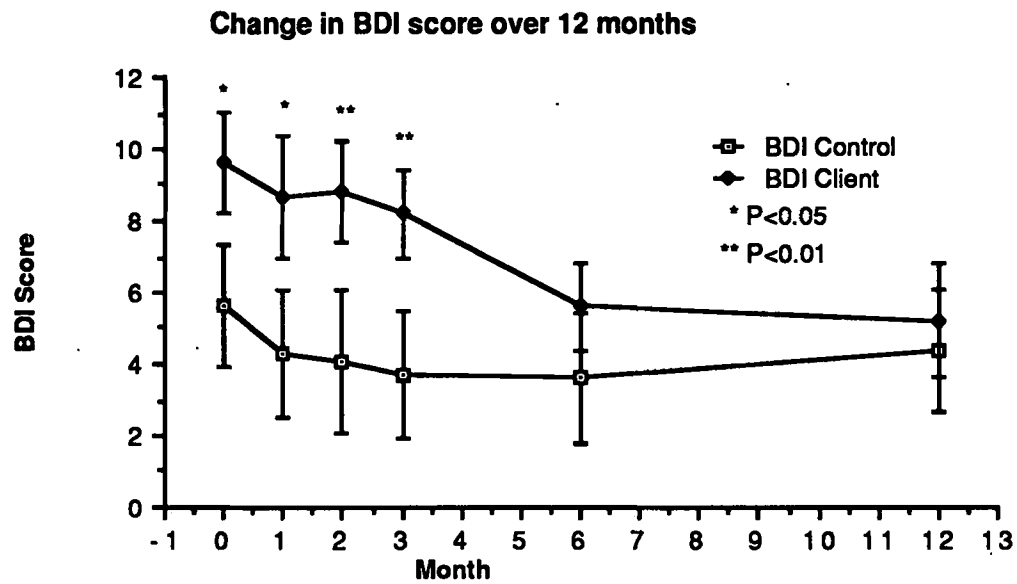
The MAACL consists of three parts:- anxiety, depression and hostility. As this study was concerned with depression with or without anxiety, hostility was removed from the scale to see whether this could in any way account for the rise at the end of the control graph. The data shown in figure 8.11 show that removing hostility did not markedly change the rise in control MAACL scores (increase score of 21% with hostility included, 23% excluding hostility). There was still no fall overall in client values although the differences observed in the scores at 6 and 12 months were no longer statistically significant.

Student t-test comparisons of the first and last (0 months and 12 months) MAACL values, either with or without the hostility score were not statistically significantly different.

It is an interesting observation that the control value is fairly stable (with or without the hostility value) up until 6 months, and that at this stage the client value appears to be falling towards the control value. I am not aware of published long term studies using the MAACL and would question whether the increased score seen in both groups at the end of treatment may be due to the effect of repeated exposure to the questionnaire. In order to investigate this an assessment was made of the number of boxes ticked by the subjects over the course of the study. It is interesting to note that whilst the number of boxes ticked by the controls remains relatively constant there is a marked decline in the number of boxes ticked by the clients. A students t-test comparing number of boxes ticked at 0 months vs 12 months indicates significantly less boxes were ticked at 12 months ($P<0.05$). The scoring of the MAACL is such that failure to tick certain 'affects' such as 'happy', scores a point (increasing the score) so it may be that at the end of the study when the clients may have been losing interest that they failed to tick as many boxes and therefore their scores remained artificially high (see fig 8.12).

Figure 8.1

The graph below shows the change in client scores on the Beck Depression Inventory compared to the control group (population 'normal') over the twelve month period of the study.

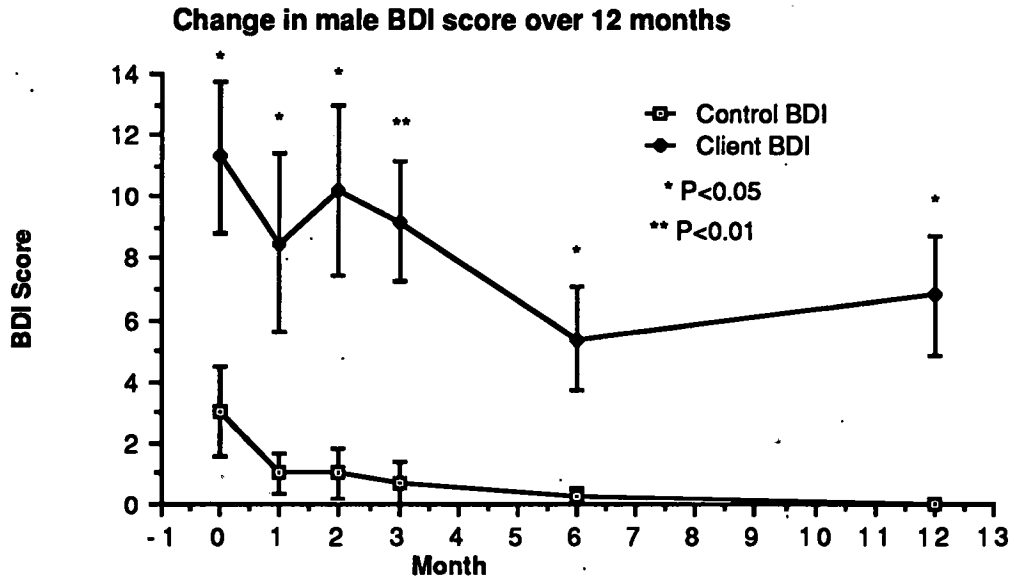


Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**
3 months **n=19;** 6 months **n=19;** 12 months **n=16.**
Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=17;**
3 months **n=19;** 6 months **n=18;** 12 months **n=16.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.2

The graph below shows the change in male client scores on the Beck Depression Inventory compared to the male control group (population 'normal') over the twelve month period of the study.

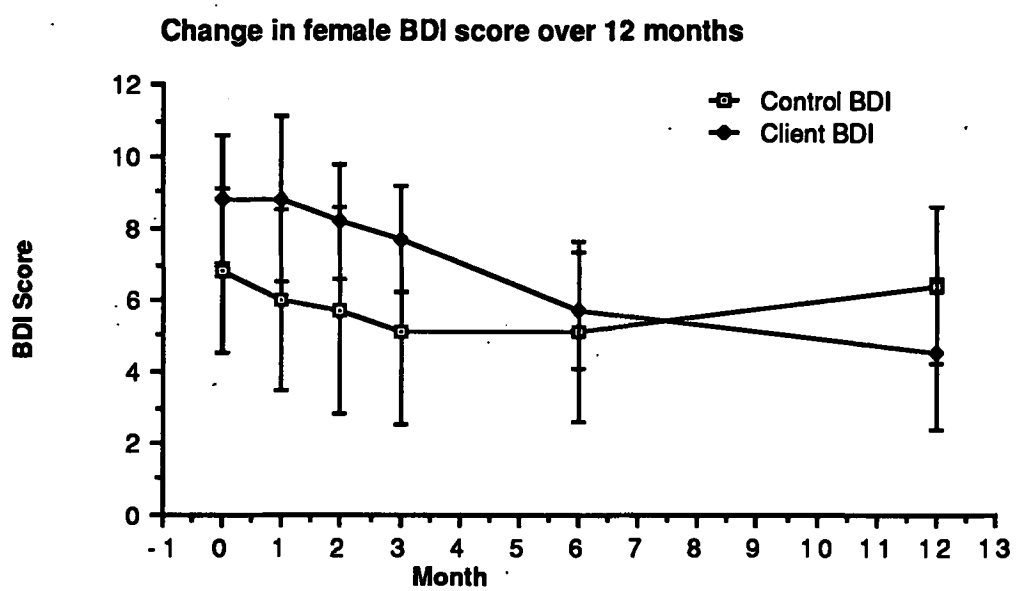


Control values: 0 months **n=6;** 1 month **n=6;** 2 months **n=6;**
3 months **n=6;** 6 months **n=6;** 12 months **n=5.**
Client values: 0 months **n=6;** 1 month **n=6;** 2 months **n=5;**
3 months **n=6;** 6 months **n=5;** 12 months **n=5.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown,were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.3

The graph below shows the change in female client scores on the Beck Depression Inventory compared to the female control group (population 'normal') over the twelve month period of the study.



Control values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**

3 months **n=13;** 6 months **n=13;** 12 months **n=11.**

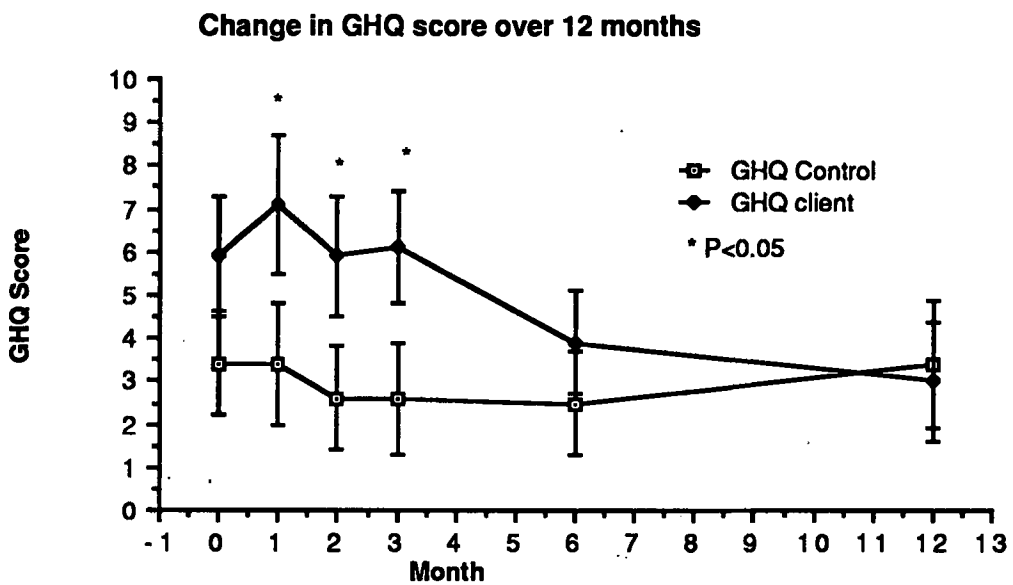
Client values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**

3 months **n=13;** 6 months **n=13;** 12 months **n=11.**

Results are expressed as means +/- standard error of mean.

Figure 8.4

The graph below shows the change in client scores on the General Health questionnaire compared to the control group (population 'normal') over the twelve month period of the study.

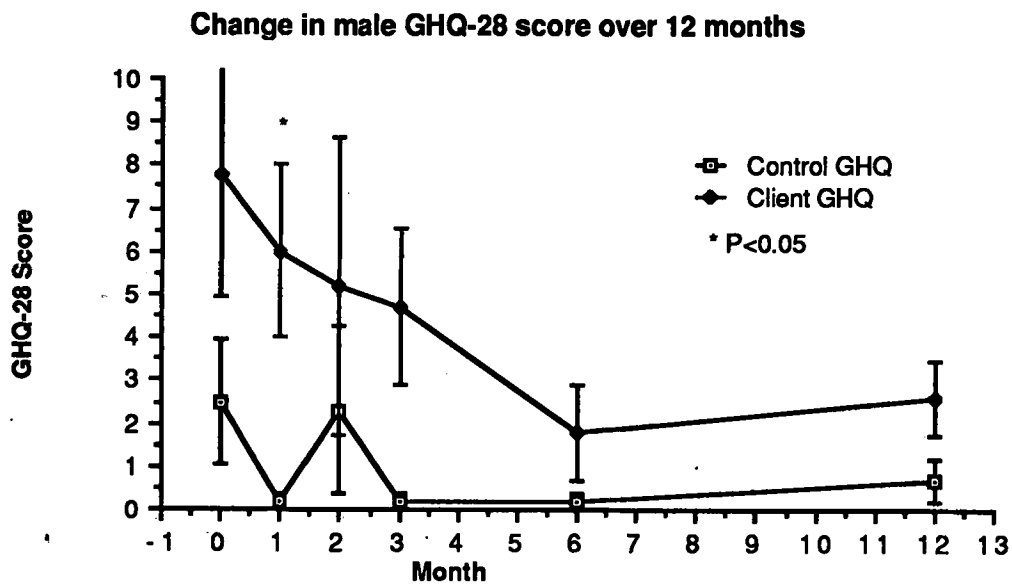


Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**
3 months **n=19;** 6 months **n=19;** 12 months **n=16.**
Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=17;**
3 months **n=19;** 6 months **n=18;** 12 months **n=16.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown,were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.5

The graph below shows the change in male client scores on the General Health Questionnaire compared to the male control group (population 'normal') over the twelve month period of the study.

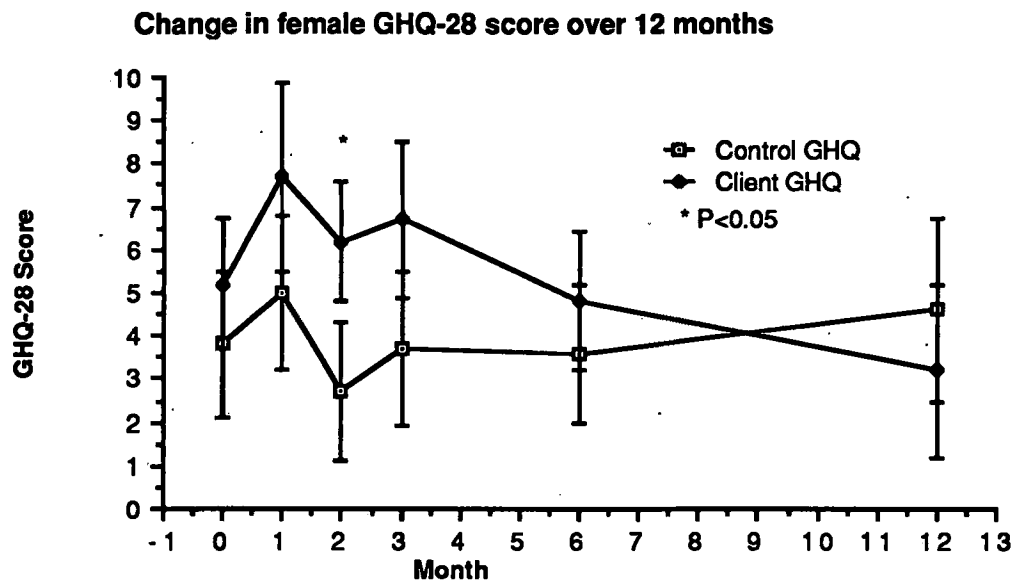


Control values: 0 months **n=6;** 1 month **n=6;** 2 months **n=6;**
3 months **n=6;** 6 months **n=6;** 12 months **n=5.**
Client values: 0 months **n=6;** 1 month **n=6;** 2 months **n=5;**
3 months **n=6;** 6 months **n=5;** 12 months **n=5.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.6

The graph below shows the change in female client scores on the General Health Questionnaire compared to the female control group (population 'normal') over the twelve month period of the study.

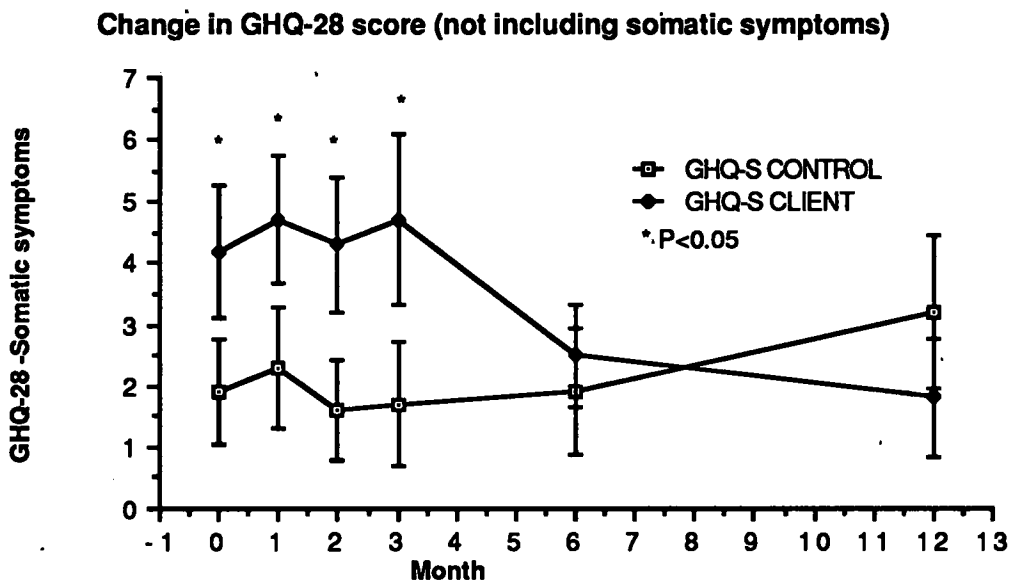


Control values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**
3 months **n=13;** 6 months **n=13;** 12 months **n=11.**
Client values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**
3 months **n=13;** 6 months **n=13;** 12 months **n=11.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown,were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.7

The graph below shows the change in client scores on the General Health Questionnaire (excluding somatic symptoms) compared to the control group (population 'normal') over the twelve month period of the study.

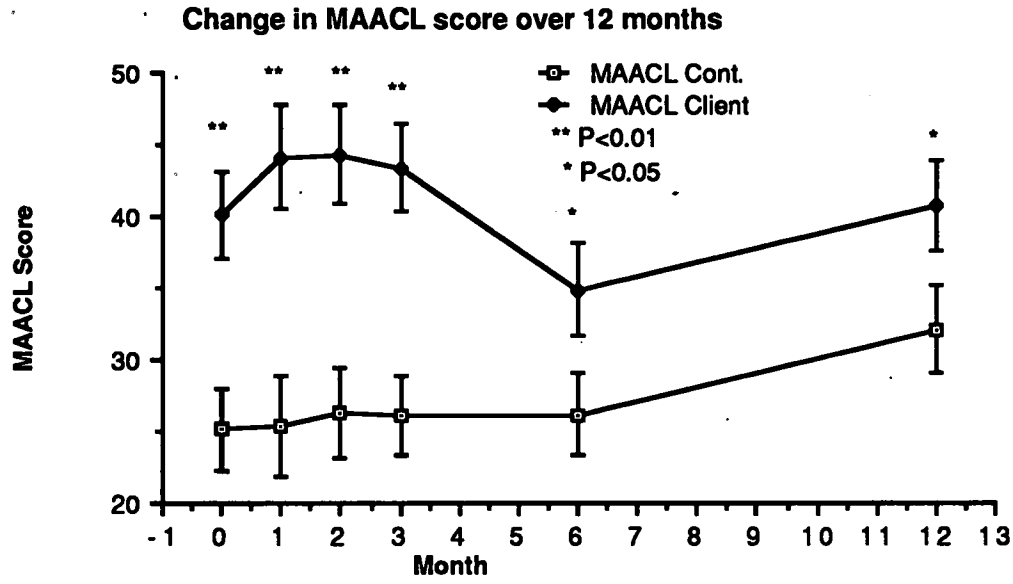


Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**
3 months **n=19;** 6 months **n=19;** 12 months **n=16.**
Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=17;**
3 months **n=19;** 6 months **n=18;** 12 months **n=16.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.8

The graph below shows the change in client scores on the Multiple Affect Adjective Checklist compared to the control group (population 'normal') over the twelve month period of the study.

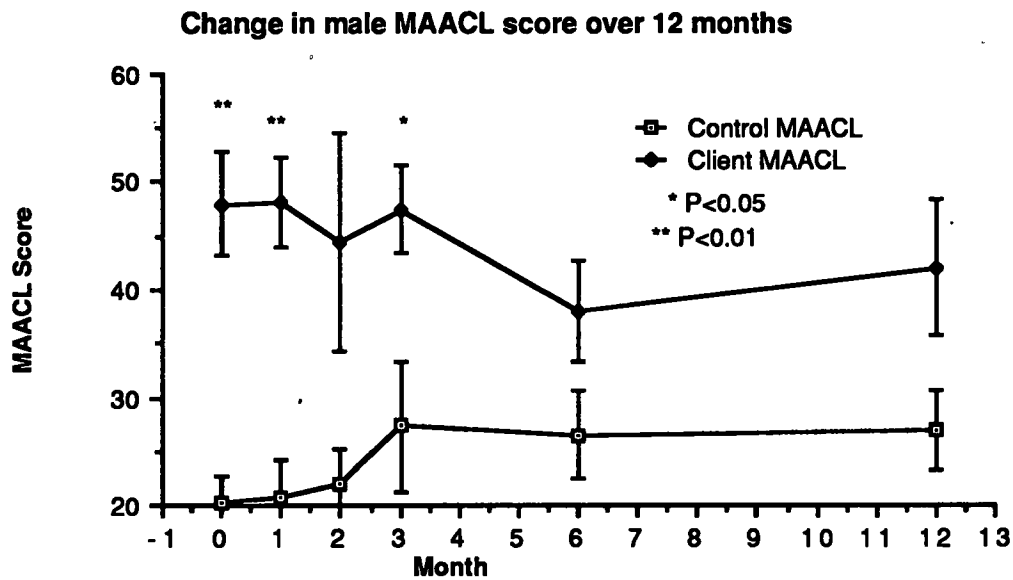


Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**
3 months **n=19;** 6 months **n=19;** 12 months **n=16.**
Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=17;**
3 months **n=19;** 6 months **n=18;** 12 months **n=16.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.9

The graph below shows the change in male client scores on the Multiple Affect Adjective Checklist compared to the male control group (population 'normal') over the twelve month period of the study.

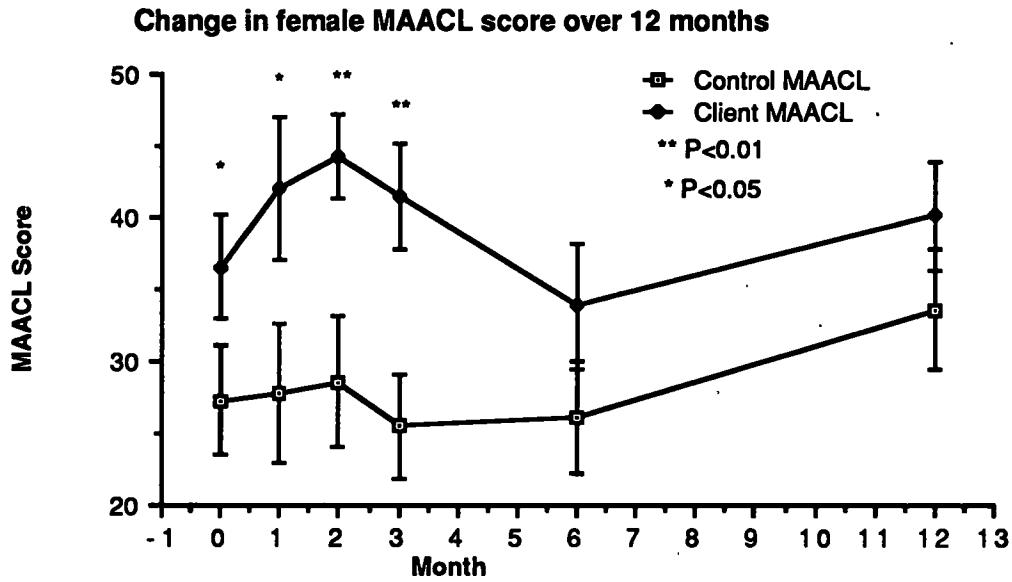


Control values: 0 months **n=6;** 1 month **n=6;** 2 months **n=6;**
3 months **n=6;** 6 months **n=6;** 12 months **n=5.**
Client values: 0 months **n=6;** 1 month **n=6;** 2 months **n=5;**
3 months **n=6;** 6 months **n=5;** 12 months **n=5.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.10

The graph below shows the change in female client scores on the Multiple Affect Adjective Checklist compared to the female control group (population 'normal') over the twelve month period of the study.

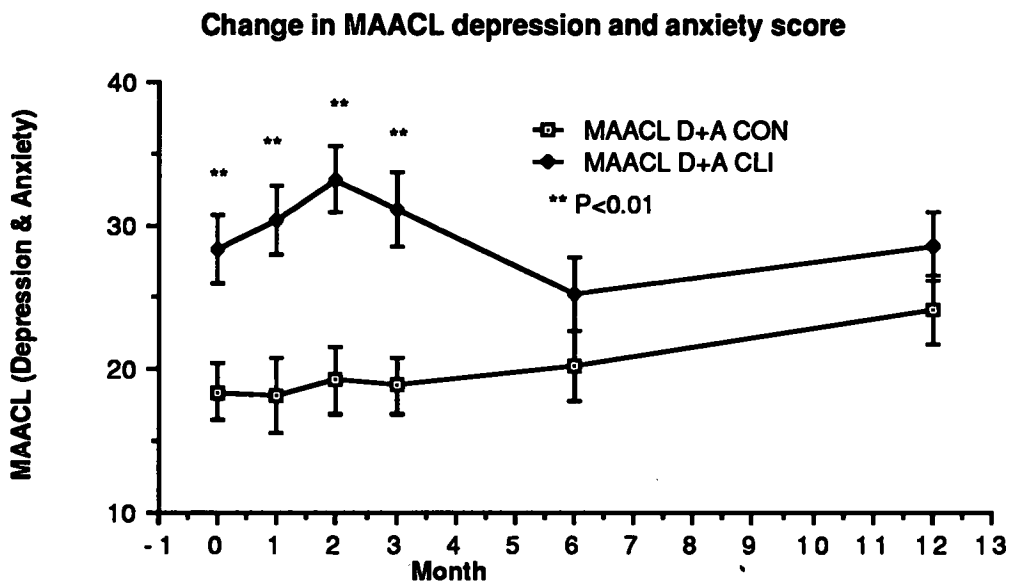


Control values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**
3 months **n=13;** 6 months **n=13;** 12 months **n=11.**
Client values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**
3 months **n=13;** 6 months **n=13;** 12 months **n=11.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.11

The graph below shows the change in client scores on the Multiple Affect Adjective Checklist (Depression and Anxiety scores only) compared to the control group (population 'normal') over the twelve month period of the study.

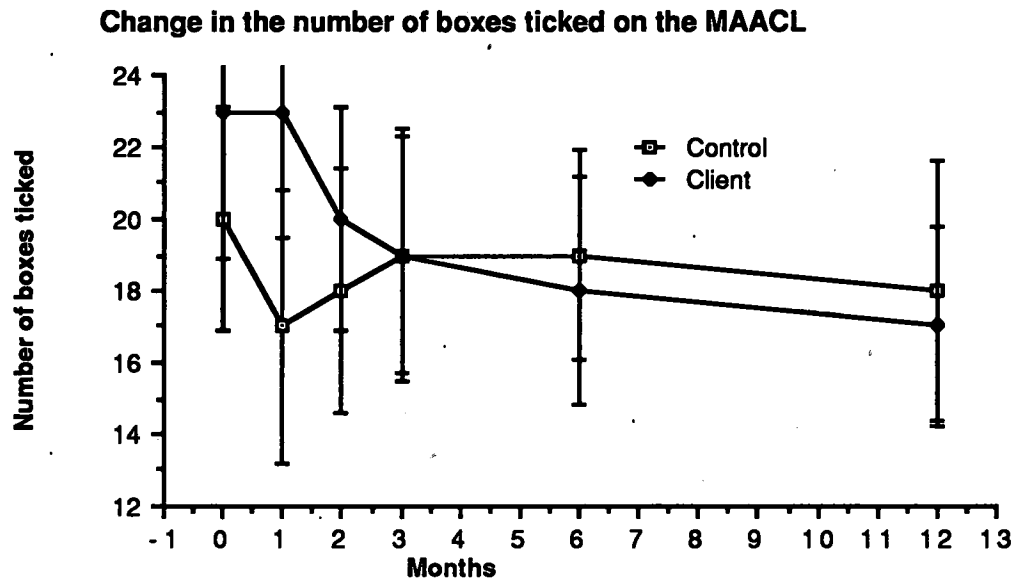


Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**
3 months **n=19;** 6 months **n=19;** 12 months **n=16.**
Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=17;**
3 months **n=19;** 6 months **n=18;** 12 months **n=16.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.12

The graph below shows the change in the number of boxes ticked on the MAACL by clients compared to the control group (population 'normal') over the twelve month period of the study.



Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**

3 months **n=19;** 6 months **n=19;** 12 months **n=16.**

Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=17;**

3 months **n=19;** 6 months **n=18;** 12 months **n=16.**

Results are expressed as means +/- standard error of mean.

Discussion of questionnaire results

Overall, the results of the questionnaires indicate a significant improvement in the psychological well being of the clients during the course of the study. It is important to emphasise that both the General Health Questionnaire and the Beck Depression Inventory are well recognised psychological testing tools (e.g. Boardman 1987; Feightner and Worrall 1990), whereas the MAACL is less well validated. Obviously with the type of control group that was used no firm conclusions can be drawn about the effectiveness of the psychotherapies. However what is clear is that the clients' psychological state improved whilst undergoing a course of psychotherapy and that although there were significant differences between client and control groups at the start of the study they were considerably diminished or possibly even reversed by the end.

What is perhaps most exciting in terms of clinical relevance is that whilst, as a group, the clients met the criteria for mild psychiatric disorder at the start of the study they did not at the end. Depression is a recurrent, cyclic illness and it could be argued that the clients may well have got better without any intervention at all. However taking into account the criteria for psychiatric caseness discussed above it is interesting to note that according to the BDI criteria no clients originally classed as 'cases' relapsed (although 2 classed as 'cases' at the beginning of the study did not improve). According to the GHQ criteria only 2 patients relapsed (and 3 originally classed as cases did not improve). Even taking the worst possible score of two out of 19 clients this only gives a relapse rate of 10.5% over 12 months. A recent report by Raffaitin *et al* (1991) reports a 22% relapse rate with Tianeptine over the same period and Jakovljevic and Mewett (1991) found a 14% relapse rate with paroxetine and 12% with imipramine compared to a 23% relapse rate with placebo. Given these data the relapse rate on this study looks particularly good. Although it should be emphasised that these patients were only mildly depressed and therefore less likely to relapse, many of them had complained to me that this was not their first experience of a depressive episode (no data were collected on the number of previous episodes). Neumann and Schuttler (1991) in a longitudinal study of depressed outpatients have shown that one year after first being treated for depression 70% of patients were still receiving tricyclic antidepressants

and that even after 5 years 60% were still taking tricyclics. Despite this however the rate of readmittance was 40%, and 50% were still suffering from psychological disorders five years later. In comparison to these data the present findings would tend to view the psychotherapeutic approach quite favourably.

An interesting observation seen in the questionnaire results is that whilst there are no very marked differences in the scores recorded by male and female clients (except possibly the GHQ-28 score), there is some evidence of a difference in control males and females particularly on the BDI. However there were relatively small numbers of males and the differences seen between males and females failed to reach statistical significance.

Changes in the binding assay results over 12 months

[^{3}H] Imipramine binding

The results from the imipramine binding assay showed that levels of imipramine binding were lower (2 months $P<0.01$) in clients from the Open centre than in controls in the early stages of treatment. Furthermore after three months of psychotherapy the levels of the client imipramine binding rose to the same, or in fact slightly higher values than the controls (see fig 8.13). A t-test performed on the client data at the start of the study versus completion of the study (0 months vs 12 months) was not, however significant. ANOVA and repeated measures ANOVA did not show any statistical difference between client and control imipramine binding during the course of the study.

Although it is generally accepted that imipramine binding is not affected by the gender of the subject(e.g. Asarch *et al* 1980), there have been differences reported (e.g. Theodorou *et al* 1989), so in order to check this the male and female data were analysed separately. When this separate analysis was carried out, the male client imipramine binding, which was lower than controls at the start of the study, was actually significantly higher ($P<0.01$) at 3 months than the controls and remained higher (see fig 8.14). However the significance of the results remained the same for the female data as for the combined data set (see Fig

8.15) and the overall pattern of results was the same for male, female and combined data, indicating that there are no major gender differences.

[^{3}H] Paroxetine binding

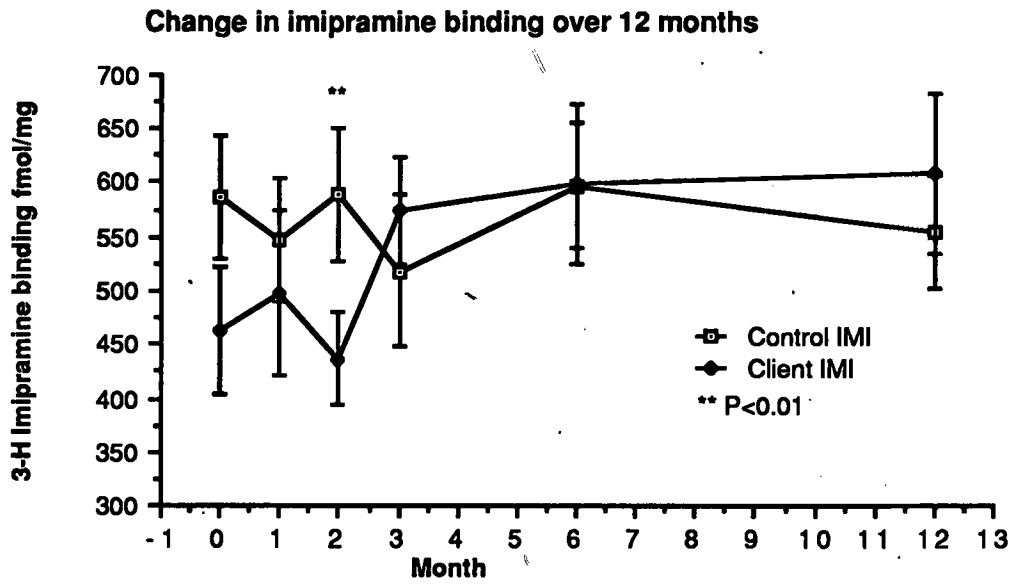
The data obtained for the paroxetine binding assay were on first inspection rather surprising. No significant difference between client and control binding levels were found at any stage during the study (see Fig 8.16). This was not what I would have predicted bearing in mind that paroxetine supposedly binds to the same sites as imipramine but with greater specificity. However this study is not the only one failing to report a difference between depressives and controls using a paroxetine binding assay (e.g.D'haenen *et al* 1988). It is possible that that the differences seen in depressives versus control subjects with imipramine binding may be related to the less specific nature of the imipramine binding or to the fact that the two compounds apparently bind to different parts of the 5HT uptake system. In a recent study of patients treated with psychoactive drugs, some drugs produced very similar changes in both paroxetine and imipramine binding, whereas others produced very different responses (Mellerup *et al* 1991)

Although paroxetine binding is not thought to be influenced by gender (Andersson and Marcusson 1990), there is some evidence of a lower binding levels in men (Klompenhouwer *et al* 1990). Therefore male and female data was analysed separately to see if any differences could be detected, however the pattern of the data was still basically the same (although males seemed to have slightly lower paroxetine binding particularly after 3 months) with no statistically significant differences apparent between clients and controls (see figs 8.17 and 8.18).

Student t-tests, ANOVA and repeated measures ANOVA, all failed to demonstrate any significant differences in client and control values during the study.

Figure 8.13

The graph below shows the change in client ^{3}H-imipramine binding to platelet membranes compared to the control group (population 'normal') over the twelve month period of the study.

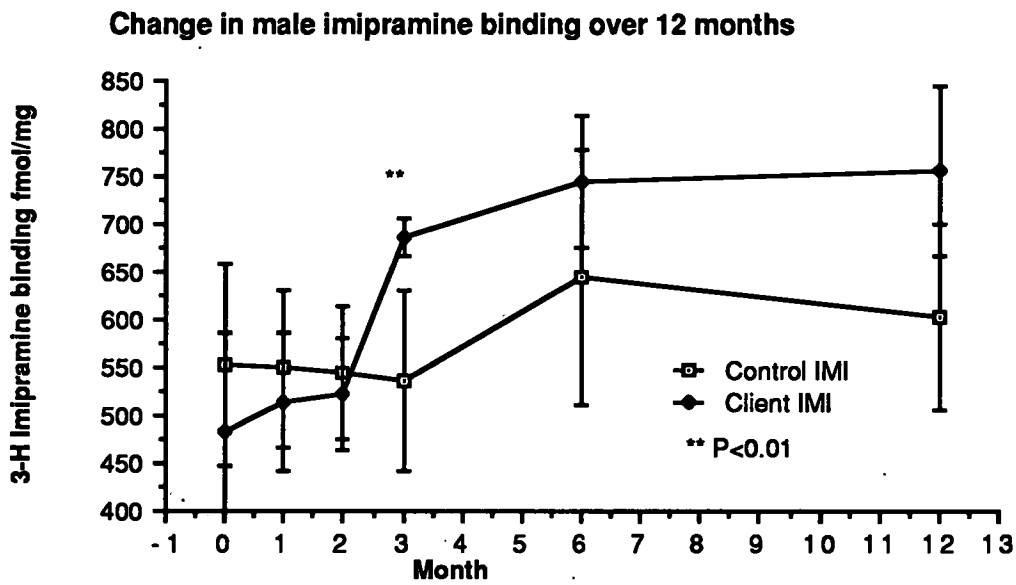


Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**
3 months **n=19;** 6 months **n=19;** 12 months **n=18.**
Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=19;**
3 months **n=19;** 6 months **n=18;** 12 months **n=18.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.14

The graph below shows the change in male client ^{3}H-imipramine binding to platelet membranes compared to the male control group (population 'normal') over the twelve month period of the study.



Control values: 0 months **n=6;** 1 month **n= 6;** 2 months **n= 6;**

3 months **n=5;** 6 months **n= 6;** 12 months **n= 6.**

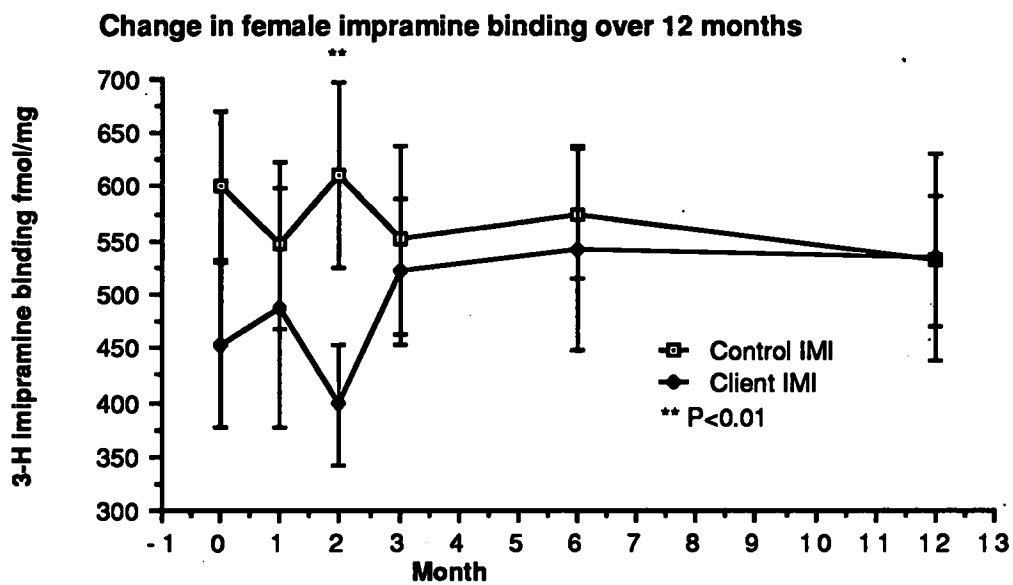
Client values: 0 months **n= 6;** 1 month **n= 6;** 2 months **n= 6;**

3 months **n= 6;** 6 months **n=5;** 12 months **n= 6.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown,were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.15

The graph below shows the change in female client ^{3}H-imipramine binding to platelet membranes compared to the female control group (population 'normal') over the twelve month period of the study.

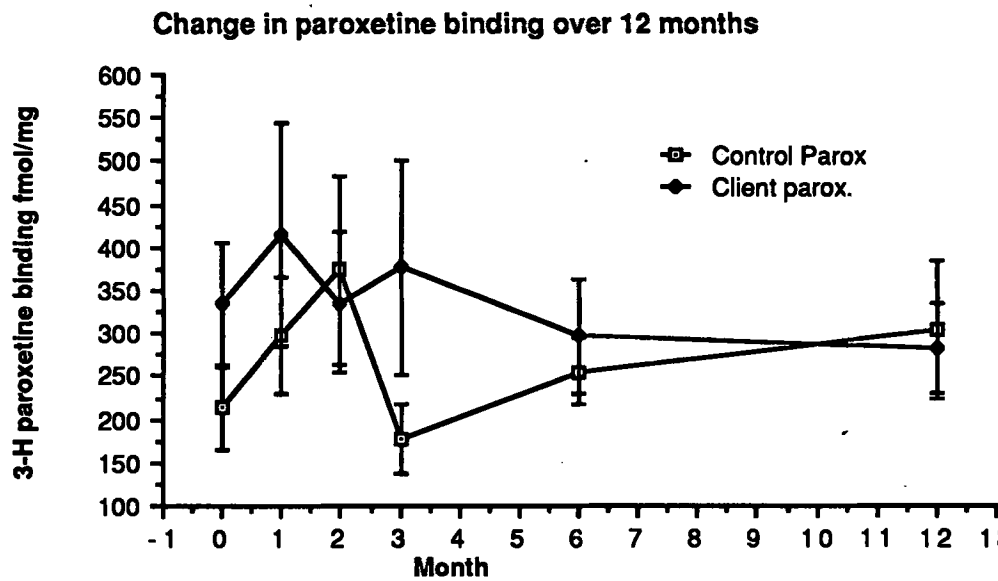


Control values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**
3 months **n=13;** 6 months **n=13;** 12 months **n=12.**
Client values: 0 months **n=13;** 1 month **n=12;** 2 months **n=13;**
3 months **n=13;** 6 months **n=13;** 12 months **n=12.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.16

The graph below shows the change in client ^{3}H-paroxetine binding to platelet membranes compared to the control group (population 'normal') over the twelve month period of the study.



Control values: 0 months **n=19;** 1 month **n=18;** 2 months **n=18;**

3 months **n=19;** 6 months **n=19;** 12 months **n=18.**

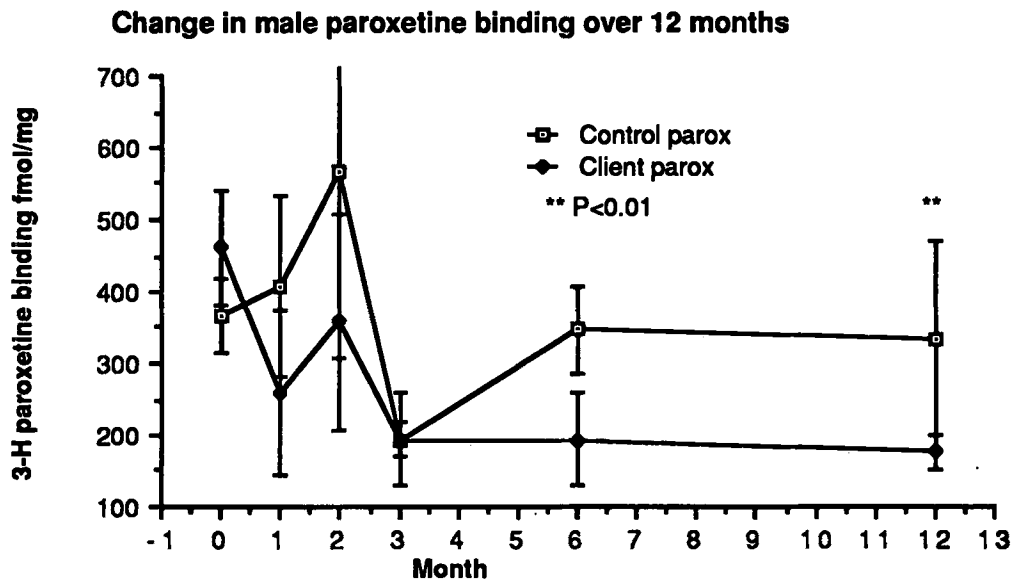
Client values: 0 months **n=19;** 1 month **n=18;** 2 months **n=19;**

3 months **n=19;** 6 months **n=18;** 12 months **n=18.**

Results are expressed as means +/- standard error of mean.

Figure 8.17

The graph below shows the change in male client ^{3}H-paroxetine binding to platelet membranes compared to the male control group (population 'normal') over the twelve month period of the study.

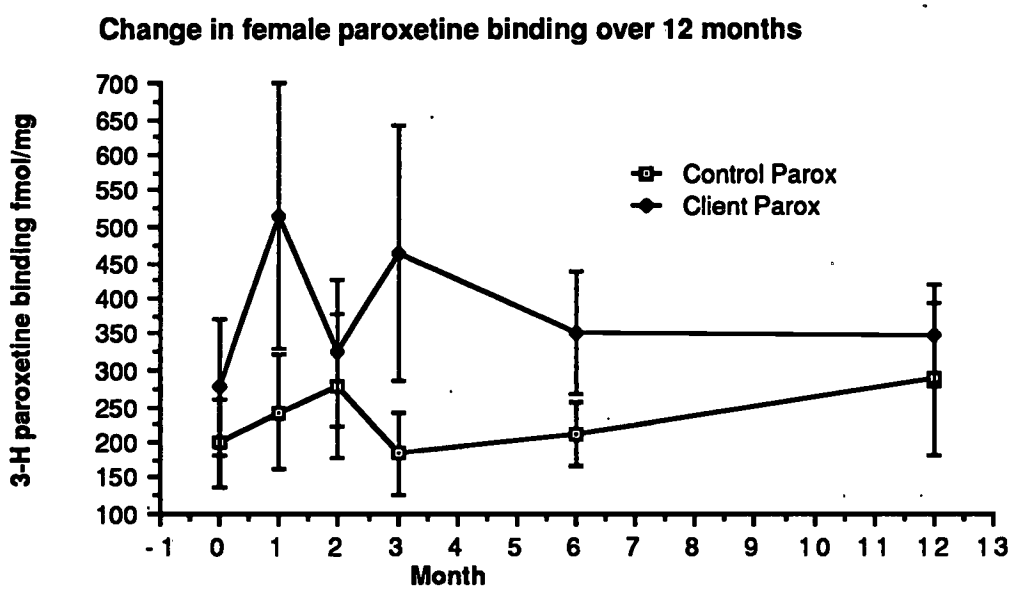


Control values: 0 months **n= 4;** 1 month **n= 6;** 2 months **n= 6;**
3 months **n= 5;** 6 months **n= 6;** 12 months **n= 6.**
Client values: 0 months **n= 6;** 1 month **n= 5;** 2 months **n= 6;**
3 months **n= 6;** 6 months **n= 4;** 12 months **n= 5.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 8.18

The graph below shows the change in female client ^{3}H-paroxetine binding to platelet membranes compared to the control group (population 'normal') over the twelve month period of the study.



Control values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**

3 months **n=13;** 6 months **n=13;** 12 months **n=12.**

Client values: 0 months **n=13;** 1 month **n=12;** 2 months **n=12;**

3 months **n=13;** 6 months **n=13;** 12 months **n=12.**

Results are expressed as means +/- standard error of mean.

Discussion of imipramine and paroxetine binding results

The imipramine binding results found in this study were the same type of results as were seen in the previous study performed in this laboratory on Primal therapy clients and is also seen as a result of a drug therapy (e.g. Healy *et al* 1991) (see Fig 8.13). Additionally Suranyi-Cadotte *et al* (1982) investigating changes in imipramine binding in 10 patients during remission, found three of these patients were not receiving any medication but showed marked increases in imipramine binding.

The differences seen between the imipramine and paroxetine binding results are quite difficult to explain. Autoradiography of binding sites for imipramine and paroxetine within the human brain indicate that the two compounds bind to the same areas of the brain (Cortes *et al* 1988; Plenge *et al* 1990). However it appears that they bind to different sites within the serotonin transport mechanism (Mellerup *et al* 1985) and different responses have been observed in imipramine and paroxetine binding in the brain after antidepressant treatment in animal studies (Plenge *et al* 1986). The different results seen between paroxetine and imipramine binding may represent a very real and important clue as to the biological systems involved in depressive disorders.

As discussed earlier, reports of decreased levels of imipramine binding to platelets of depressed patients are numerous (e.g. Langer *et al* 1987; Benkelfat *et al* 1985; Jeaningros *et al* 1989; Poirier *et al* 1986; De Met *et al* 1991). It has also been shown that these binding levels can be increased by treatment with antidepressants (e.g. Asberg and Wagner 1986; Healy *et al* 1991), light therapy (Szadoczky *et al* 1989), ECT (Langer *et al* 1980) and oestrogen therapy (Sherwin and Suranyi-Cadotte 1990).It is also fairly well established that serotonin turnover may be reduced by up to 40% in these patients (Kalus *et al* 1989). However there has not been any evidence of decreased paroxetine binding in depressed patients (D'haenen *et al* 1988), and work in suicides has found no difference in paroxetine binding whilst demonstrating differences in imipramine binding (Lawrence *et al* 1990). Some authors have argued that since paroxetine binding assays are conducted at the physiological temperature of 37^0C (whereas the imipramine binding assay is conducted on

ice) that paroxetine binding may better reflect 5HT uptake sites (Schoemaker *et al* 1986). Furthermore, whilst imipramine binding has generally been found to be reduced in depressed patients (presumably representing a decrease in 5HT uptake sites) it has proved difficult to correlate these findings with 5HT uptake from the same patients (e.g. Raisman *et al* 1982: Suranyi-Cadotte *et al* 1982), although reduced 5HT uptake in depressed patients is widely reported (e.g. Egrise *et al* 1986).One possible explanation for the differences seen with imipramine and paroxetine binding that cannot be excluded, is that the platelets used for the imipramine assay were originally intended for a clonidine assay and so were treated differently. this could have resulted in differences in the quality of the membrane preparations and possibly the proportion of intact platelets which would influence the observed binding (DeMet *et al* 1990).

What remains clear is that 5HT is almost undoubtedly involved in affective disorders as evidenced by the number of 5HT uptake inhibitors gaining popularity in the treatment of depression, and 5HT antagonists being developed for the treatment of anxiety. Recently attempts to correlate plasma levels of imipramine with response have finally proved successful (Garvey *et al* 1991). Deakin (1991) (Also Deakin and Graeff 1991) proposed a theory of 5HT involvement in affective disorders where anxiety results from dysfunctional activation of anticipatory defence mechanisms leading to excessive stimulation of $5HT_2$, $_{1C}$ and $_3$ receptors in the amygdala and other forebrain structures by the dorsal raphe 5HT projections. Whereas depression results from attenuation of chronic defensive responses mediated by median raphe projections causing a decrease in 5HT1A neurotransmission. Although acceptance of a 5HT involvement in depression predominates it can in no way account for the differences seen in imipramine and paroxetine binding. What this theory does emphasise however is the extensiveness of the serotonergic system. In addition to this it should be remembered that the serotonergic system does not function in isolation, indeed there is evidence that imipramine may actually function as an antidepressant, not by inhibition of 5HT uptake but by down regulation of β-adrenergic receptors. The evidence for the interrelation of adrenergic and serotonergic systems being quite strong (Eison *et al* 1991; Plaznik *et al* 1989). This would, it is argued account for the slow onset of action of

imipramine (Beck and Halloran 1989).

Malmgren *et al* (1981) demonstrated that platelets of depressed patients had defective transport mechanisms for 5HT. It also appears that the antidepressant binding sites are the same as the uptake sites (Marcusson *et al* 1989).It is possible that the part of the uptake site which imipramine binds to is defective and limits binding, whereas the part of the site which paroxetine binds to may be unaffected. If these 'damaged' uptake sites were also incapable of 5HT uptake this would account for the comparable efficacy of imipramine and paroxetine in the treatment of depression. It is also possible that these two sites are differently affected in the brain from the platelets, so that we may not actually be observing the true picture by conducting platelet studies.

As discussed previously a number of researchers have suggested that imipramine binding represents a trait marker for depression (e.g. Baron *et al* 1986). The results from this study do not support this hypothesis as the clients imipramine score clearly improved during therapy, I would therefore agree with the theory that imipramine is a state dependent marker of depression (as indicated by other research e.g. Langer *et al* 1986), but whether or not it is actually truly representative of serotonergic function requires further investigation. Interestingly, decreased imipramine binding has now been demonstrated in patients suffering from premenstrual syndrome immediately prior to development of the symptoms and returns to normal after menstruation (Rojansky *et al* 1991)

Paroxetine on the other hand appears not to be a marker of affective disorders at least in this population

Correlations between binding assays and questionnaires

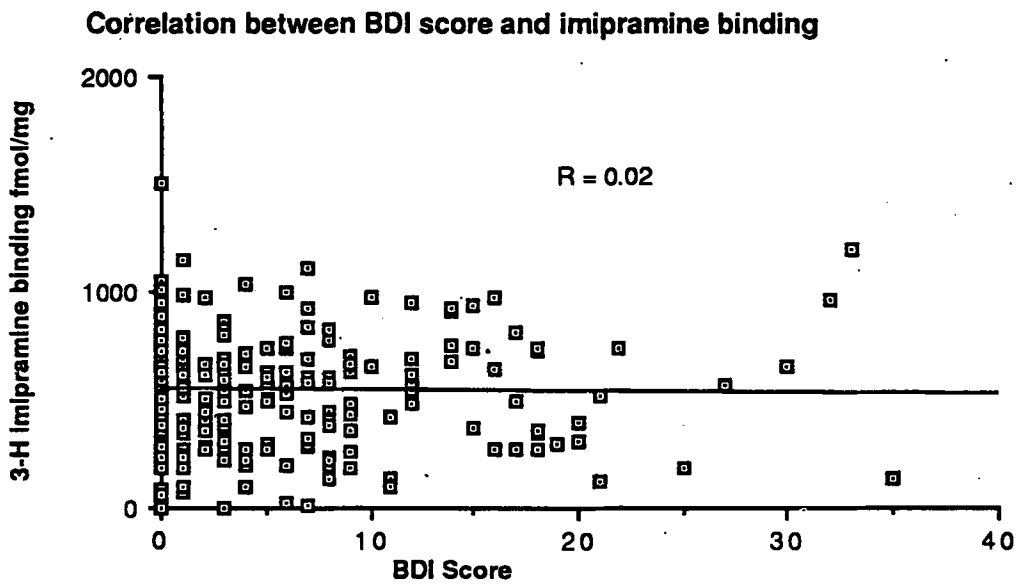
One aim of this research was to try and demonstrate a correlation between changes in imipramine/paroxetine binding with changes in questionnaire values. Since both imipramine binding and questionnaire values changed over the time and on roughly the same timescale a correlation might have been expected. However there was no correlation

between paroxetine/imipramine binding and the questionnaires (the same effect is seen if client and control values are looked at independently) See figs 8.19-8.24.

As well as attempting to correlate actual questionnaire values with imipramine and paroxetine binding, change since last assessment and change from baseline were also compared with no significant correlation being found.

Figure 8.19

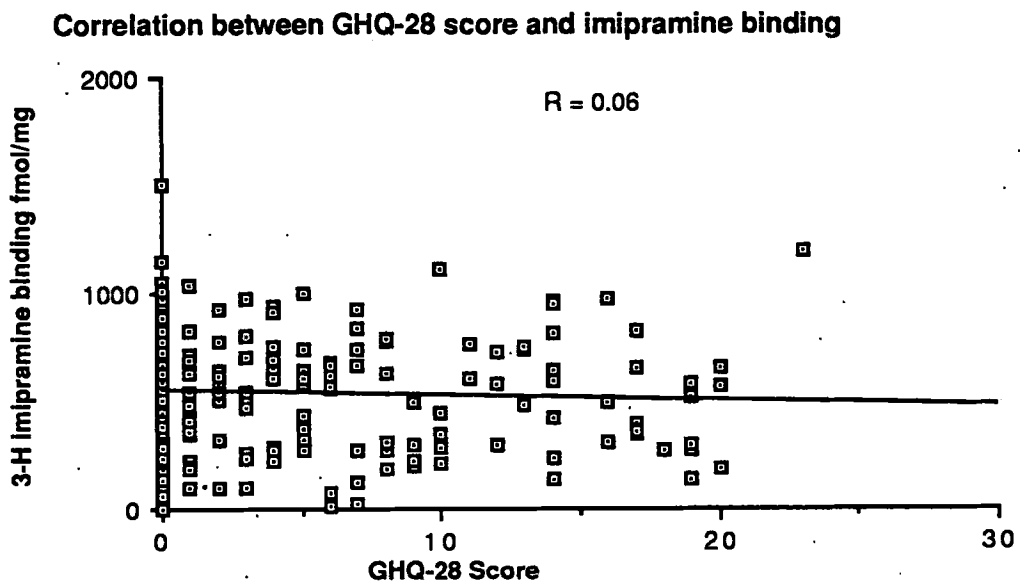
The graph below shows the level of correlation between BDI scores and imipramine binding.



The results shown are from client and control results. No correlation is apparent.

Figure 8.20

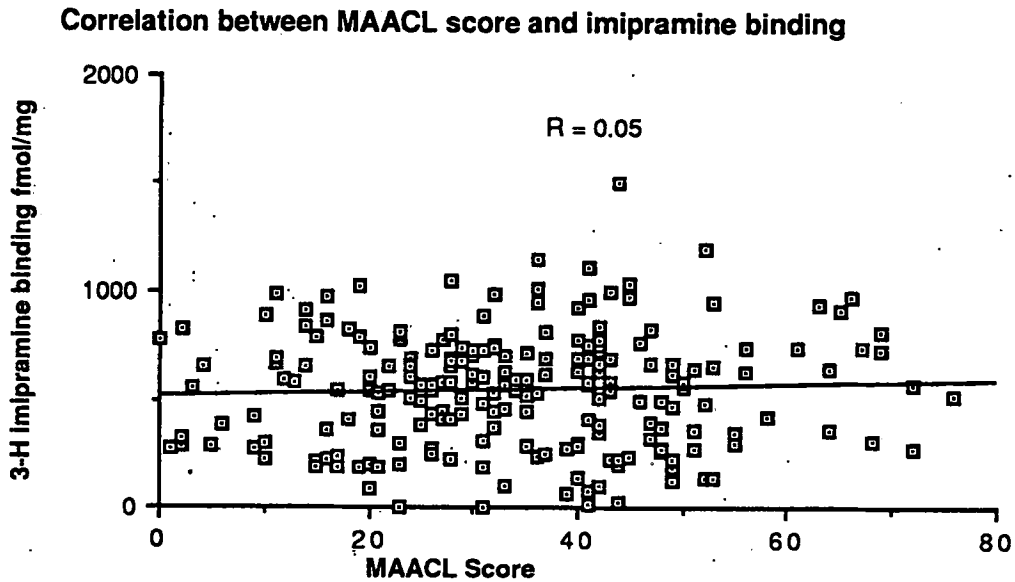
The graph below shows the level of correlation between GHQ-28 scores and imipramine binding.



The results shown are from client and control results. No correlation is apparent.

Figure 8.21

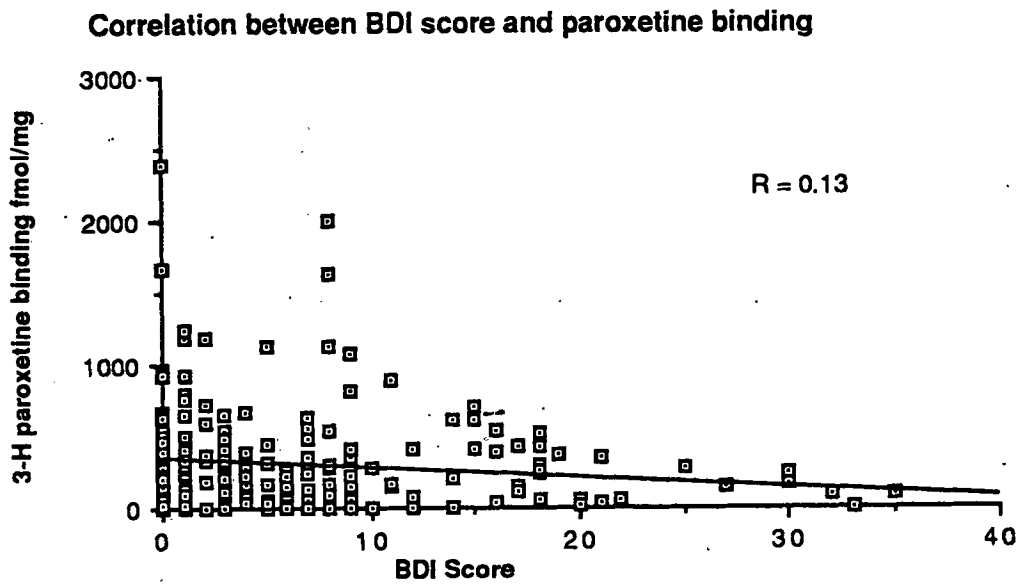
The graph below shows the level of correlation between MAACL scores and imipramine binding.



The results shown are from client and control results. No correlation is apparent.

Figure 8.22

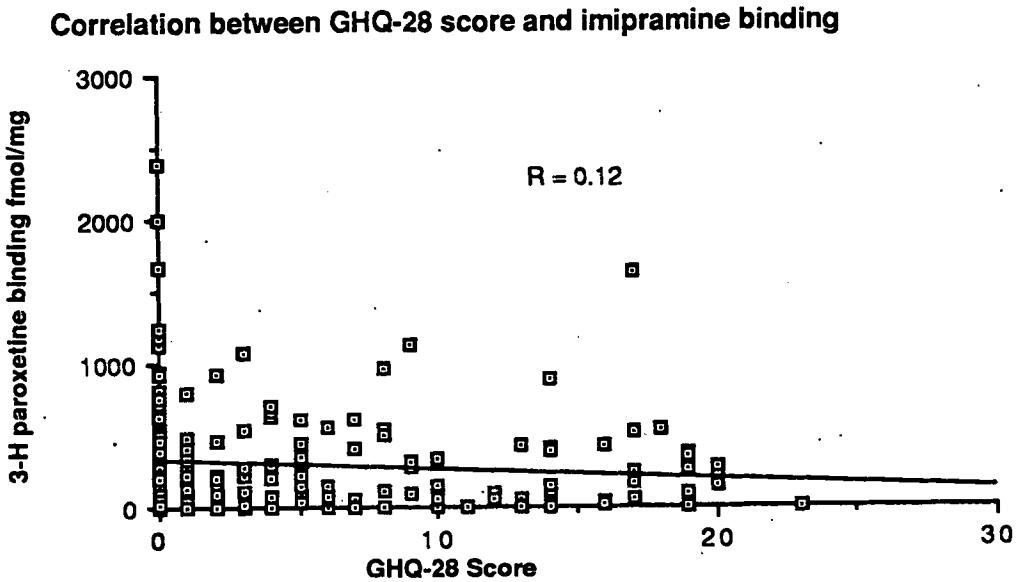
The graph below shows the level of correlation between BDI scores and paroxetine binding.



The results shown are from client and control results. No correlation is apparent.

Figure 8.23

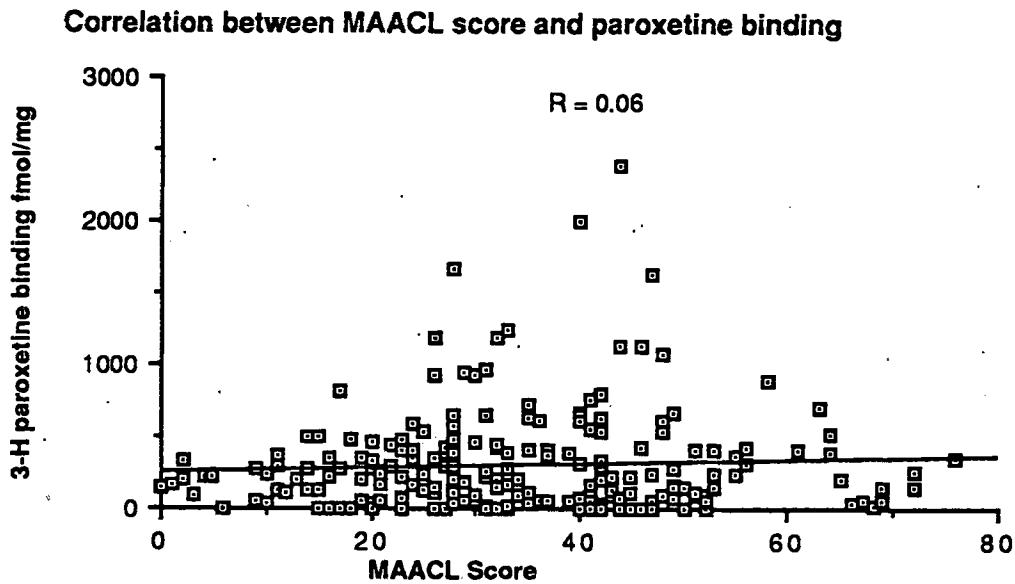
The graph below shows the level of correlation between GHQ-28 scores and paroxetine binding.



The results shown are from client and control results. No correlation is apparent.

Figure 8.24

The graph below shows the level of correlation between MAACL scores and paroxetine binding.



The results shown are from client and control results. No correlation is apparent.

Discussion of correlation data

Why no correlations are apparent is not clear,but has been found by several other investigators (e.g. De Met *et al* 1990; 1991), and may possibly represent either a delay in imipramine binding response or early imipramine binding response before the change is observable in the client, such as might be seen if alteration in a second receptor (e.g. β-adrenoceptor) actually bought about the clinical change. Another possibility is that in some clients imipramine binding may actually have decreased as their questionnaire scores decreased. This has been observed in some drug studies and is generally believed to be a direct effect of the drug action, but it may be that different people respond in different ways depending on the type of treatment and that this may represent an indicator for patients most likely to relapse.

To take this argument further, imipramine binding levels are generally accepted to be decreased in depressed patients. This is believed to represent diminished 5HT function at the synapse. To treat depression psychiatrists administer 5HT uptake blockers which allow levels of 5HT at the synapse to increase thus increasing post synaptic stimulation. This means that there are two ways a patient could improve with or without the intervention of drug therapy. The first is a genuine increase in 5HT activity at the synapse. This would result in an increase of 5HT uptake sites required to take up the 5HT. This is what is seen in studies where imipramine binding increases with drug therapy. Alternatively there may be a type of temporary coping mechanism employed by some subjects where 5HT uptake sites actually decrease in number. This would temporarily restore the level of 5HT at the synapse, until the uptake sites can no longer decrease in number, and 5HT levels continue to decrease resulting in depression. It would be these subjects that are most likely to relapse.

Seasonality of the data

1) Imipramine

A number of workers have reported seasonal changes in imipramine binding and serotonin uptake, with lower values reported in autumn and winter months (e.g. Hrdina *et al* 1985; Egrise *et al* 1986; Arora *et al* 1984; Malmgren *et al* 1989). It was not a primary aim of this study to look at seasonality and so clients and controls were not assessed evenly over the course of a calendar year. Most data was collected from February through to September (data for January, July, October, November and December was from 5 or less clients or controls). It is interesting to note however that there does seem to be a tendency for imipramine binding values to rise over the course of a calendar year and are highest around October as seen in several other investigations (e.g.Arora and Meltzer 1988; Egrise *et al* 1983; Whitaker *et al* 1984). (see fig 8.25). However as most clients started the study in the spring it is likely that their increased imipramine binding over the course of the year represents improved psychological state rather than a true effect of season. Other investigators, have also not found any evidence of seasonality e.g. Tang and Morris (1985), and Galzin *et al* (1986).

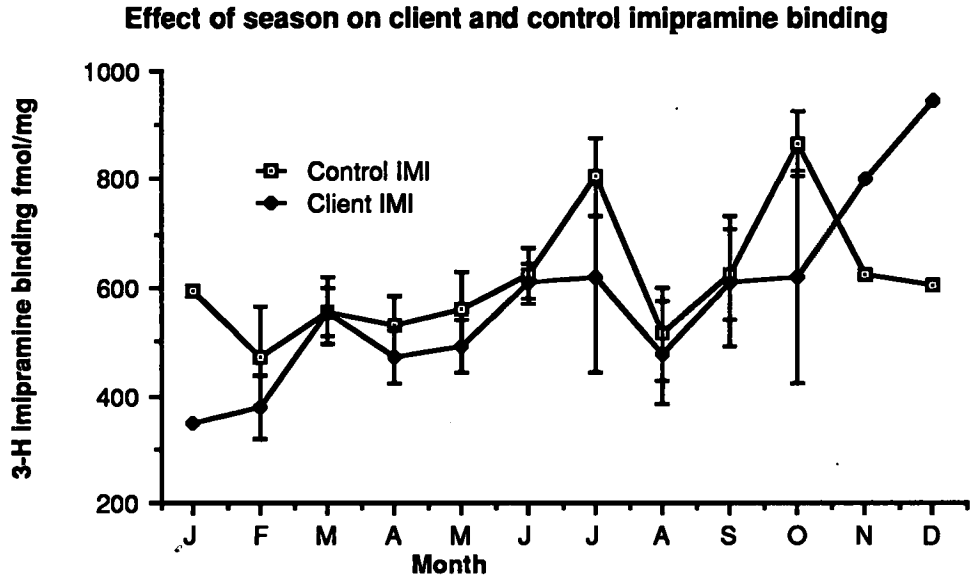
When the client and control data were combined there was still no strong evidence of seasonality (see fig 8.26).

2) Paroxetine

Although relatively little work has been done to investigate seasonal changes in paroxetine binding there is some evidence of seasonal fluctuations (Klompenhouwer *et al* 1990). From work on rabbits it appears that paroxetine binding is susceptible to circadian variation (Rocca *et al* 1989), which might suggest that it could also be influenced by daylength and therefore season. However from the present results, the paroxetine data appears to be fairly stable over the year (see figure 8.27). It was also not affected by combining the client and control data (see fig 8.28)

Figure 8.25

The graph below shows the effect of seasonality on client and control imipramine binding.



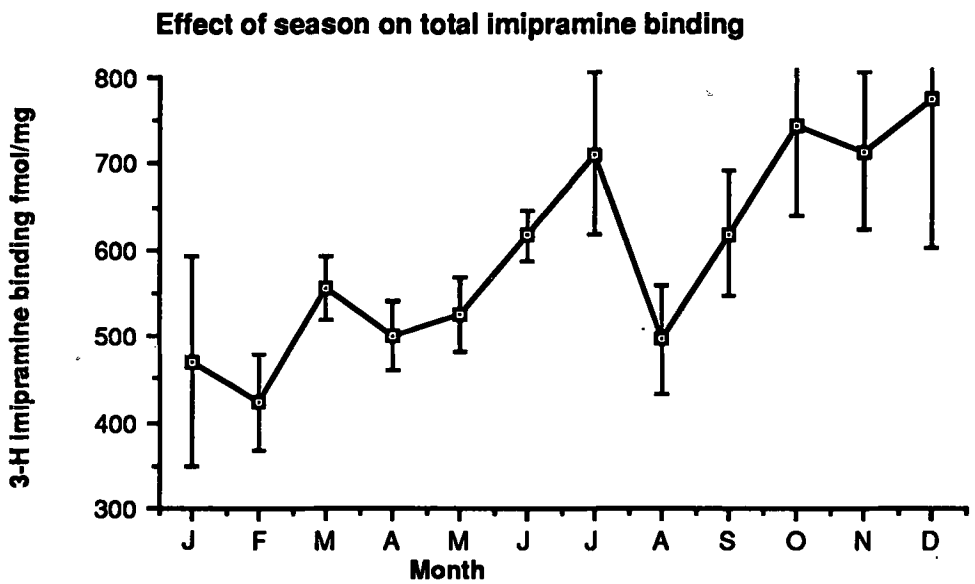
Control values: Jan **n=1**; Feb **n=1**; Mar **n=29**; Apr **n=18**; May **n=16**; Jun **n=7**; Jul **n=3**; Aug **n=9**; Sep **n=8**; Oct **n=4**; Nov **n=1**; Dec **n=1.**

Client values: Jan **n=1**; Feb **n=1**; Mar **n=29**; Apr **n=19**; May **n=16**; Jun **n=8**; Jul **n=3**; Aug **n=9**; Sep **n=8**; Oct **n=4**; Nov **n=1**; Dec **n=1.**

Results are expressed as means +/- standard error of mean.

Figure 8.26

The graph below shows the effect of seasonality on combined client and control imipramine binding.

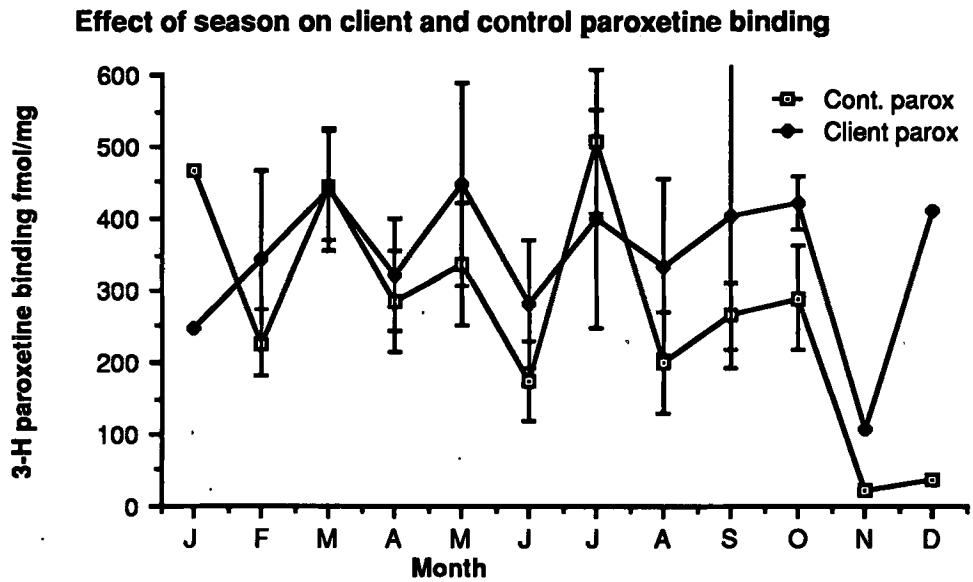


n values are a combination of the values on the previous figure.

Results are expressed as means +/- standard error of mean.

Figure 8.27

The graph below shows the effect of seasonality on client and control paroxetine binding.



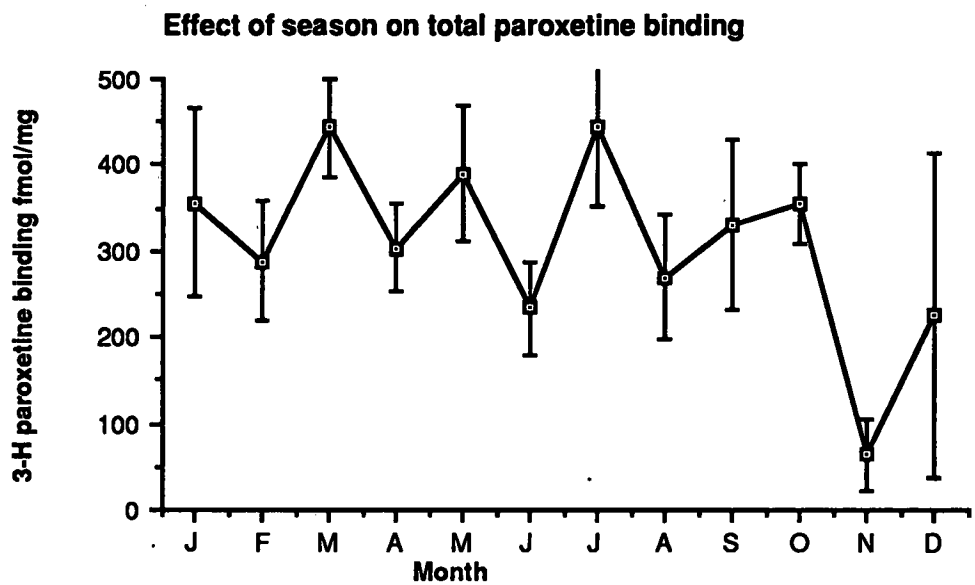
Control values: Jan **n=1**; Feb **n=1**; Mar **n=29**; Apr **n=18**; May **n=16**; Jun **n=7**; Jul **n=3**; Aug **n=9**; Sep **n=8**; Oct **n=4**; Nov **n=1**; Dec **n=1.**

Client values: Jan **n=1**; Feb **n=1**; Mar **n=29**; Apr **n=19**; May **n=16**; Jun **n=8**; Jul **n=3**; Aug **n=9**; Sep **n=8**; Oct **n=4**; Nov **n=1**; Dec **n=1.**

Results are expressed as means +/- standard error of mean.

Figure 8.28

The graph below shows the effect of seasonality on combined client and control paroxetine binding.



n values are a combination of the values on the previous figure.

Results are expressed as means +/- standard error of mean.

Discussion of seasonality data

These data do not provide any clear evidence for seasonal changes in imipramine or paroxetine binding. Although there appears to be a change in paroxetine binding towards the end of the year it should be emphasised that the last two points are from one client and one control each. The reason that no seasonality is apparent may very probably be due to the fact that I wasn't actually looking for it. It could be more interesting to look at imipramine binding in patients with seasonal affective disorder and see how their imipramine binding changes over 12 months.

Patients suffering from seasonal affective disorders have been shown to respond to light therapy (Terman *et al* 1991), some authors have argued that the white light exposure needs to be made early in the morning (Wirz-Justice 1986), whereas others have utilised evening white light therapy (Grota *et al* 1989). However this therapy is not effective in non-seasonal disorder (Wirz-Justice 1986; Mackert *et al* 1991). Other workers have demonstrated distinct physiological responses to bright light therapy indicative of an antidepressant effect (review by Dilsaver 1989). Changes in imipramine binding to platelets of these patients after bright light therapy has also been observed in parallel with clinical improvement (Szadoczy *et al* 1989) so it may be that studies which have shown evidence of seasonal changes actually reflect different light levels.

These findings of change in imipramine binding as a result of changing light levels is also supported by work which shows elevated imipramine binding in the hypothalamus of rats exposed to a reverse dark:light regime of 10:14 (Rovescalli *et al* 1989).

CONCLUSIONS

The first prediction of this study was that on entry clients would have lower imipramine and or paroxetine binding levels than controls and that during the course of psychotherapy their binding levels would increase to equal that of the control values. This prediction was proved true for imipramine but not for paroxetine.

The second major prediction was that it should be possible to correlate imipramine and paroxetine binding with questionnaire scores, in the event this did not prove to be the case, and no correlations were obtained.

CHAPTER 9

RESULTS FROM THE NURSES (UNTREATED CONTROL) GROUP.

The results presented in this chapter are from the group of nurses compared to the same control group as was used for the psychotherapy clients. Even though they were not specifically matched for age and gender, they were fairly similar except for the fact that there were less males in the nurses group.

Table 9.1. Age and gender of subjects.

	Nurses (N=27)	Controls (N=19)
Age: Mean	30	36
Range	21-55	23-49
Sex: % female	89	68

Generally the nursing staff were too busy to complete the questionnaires at the time of my visit and so it was agreed that they would complete them that day and return them to me at the next visit. It is an interesting observation that all questionnaires returned were from female nurses (with the exception of one male set of questionnaires at 0 months).

Changes seen in the questionnaire scores

Beck Depression Inventory (BDI)

Control values on the BDI were statistically significantly higher than the nurses values throughout the twelve month period except for the 6 month time point where statistical

significance was not reached (0,1 and 2 months P<0.01; 3 and 12 months P<0.01). This would apparently indicate that the control group was more depressed than the nurses (see fig 91). This was not what was predicted as there are a large number of publications showing that nurses are in a stressful occupation and are likely to show higher levels of psychiatric disorder than a control population, e.g Livingstone and Livingstone (1984), Wolfgang (1988) and McCue (1986).

Comparison of baseline and 12 month data revealed no change over time for the nurses data. When female data alone was analysed a similar pattern of results was seen but the differences reached statistical significance at all time points, which presumably reflects the higher value of female control BDI data.(0,1,2,3 and 12 months P<0.01; 6 months P<0.05), see figure 8.2. Male data were not analysed separately as there was insufficient male nurses data. ANOVA and repeated measures ANOVA did not reveal any statistically significant differences in the control and Nurses group over time.

General Health Questionnaire 28 (GHQ-28)

GHQ-28 values for the nurses were generally lower than controls (indicating greater psychological well-being) although only reaching statistical significance at 0 and 1 month (0 month P<0.05; 1 month P<0.01). Although statistical significance was only reached at the first two time points, the graph does not look as though the two sets of data are actually diverging (see figure 9.3). As with the BDI this is completely opposite to what would have been predicted from knowledge about levels of stress experienced by nurses.

There was no significant change in GHQ-28 scores over time, when analysed by t-test or ANOVA and repeated measures ANOVA . When female data alone was compared a significant difference was observed at 2 and 12 months as well as 0 and 1 month (0 and 1 month P<0.01; 2 and 12 month P<0.05). Overall however the pattern of results was the same, and a gender difference was not apparent (see fig 9.4). As with the BDI male data were not analysed separately.

As with the client and control data, the data from the GHQ-28 were also analysed in the absence of somatic symptoms (see previous chapter). Scores for the nurses were still markedly lower than the control values and reached statistical significance ($P<0.01$) at 1 month and 12 months (see fig 9.5).

There was no significant change in the GHQ, excluding the somatic symptoms score over the time course of the study.

Multiple Affect Adjective Checklist (MAACL)

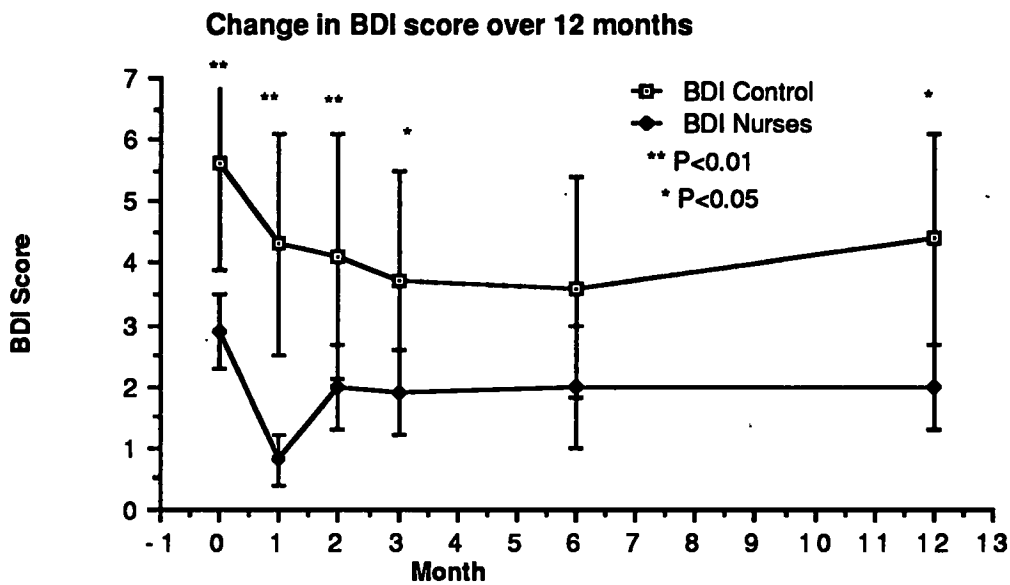
Nurses scores on the MAACL were approximately the same as control values except for the 2 month assessment ($P<0.01$) when the nurses values drop suddenly and 12 month assessment when the control value increases sharply. As discussed in the previous chapter there is no clear explanation for the sudden rise in control values at 12 months. It is also not clear why there is a sudden fall in nurses values at 2 months. (see figure 8.6)

There was no significant change in nurses MAACL score over time. When the female results were analysed alone the same pattern of results was seen as above with a statistically significant difference being seen at 2 months ($p<0.01$) but at no other time point (see figure 9.7). Male nurses MAACL data were not analysed separately due to insufficient data.

As with the client and control scores it was considered useful to look at the depression and anxiety sub-scales of the MAACL on their own. The data shown in figure 9.8 indicate that removing hostility did not markedly alter the relative value of the results, although the difference seen at 2 months was lessened (see Fig 9.8). There was no significant change in nurses anxiety and depression sub-scores of the MAACL over time.

Figure 9.1

The graph below shows the change in nurses scores on the Beck Depression Inventory compared to the control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.1

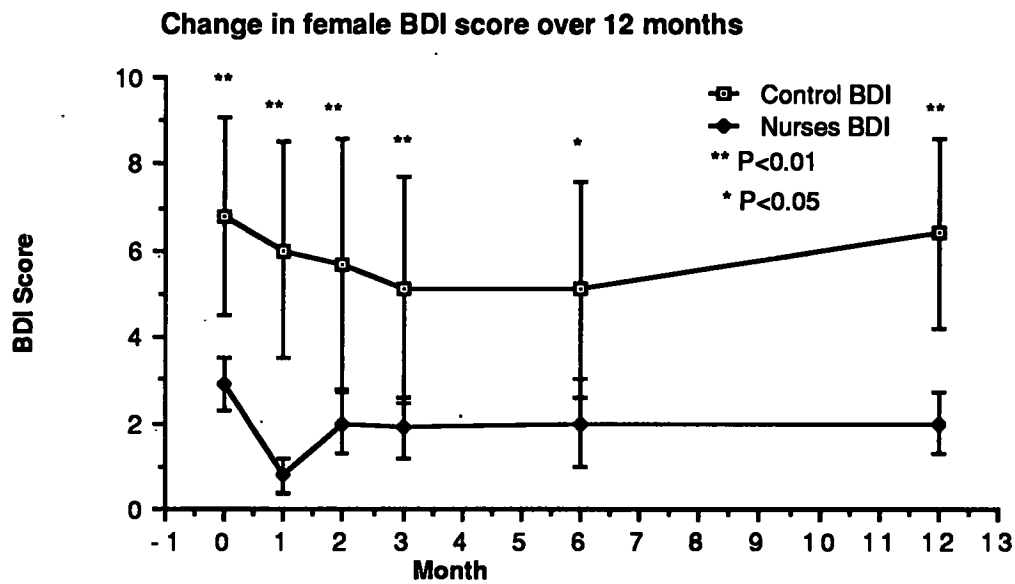
Nurses values: 0 months **n=23;** 1 month **n=13;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown,were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.2

The graph below shows the change in female nurses scores on the Beck Depression Inventory compared to the female control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.3

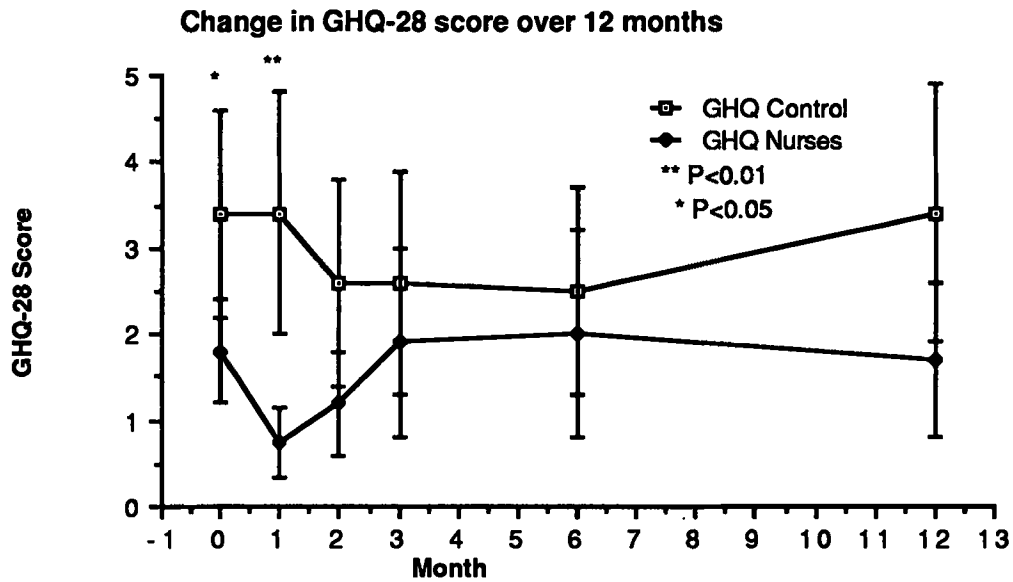
Nurses values: 0 months **n=23;** 1 month **n=13;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.3

The graph below shows the change in nurses scores on the General Health Questionnaire compared to the control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.4

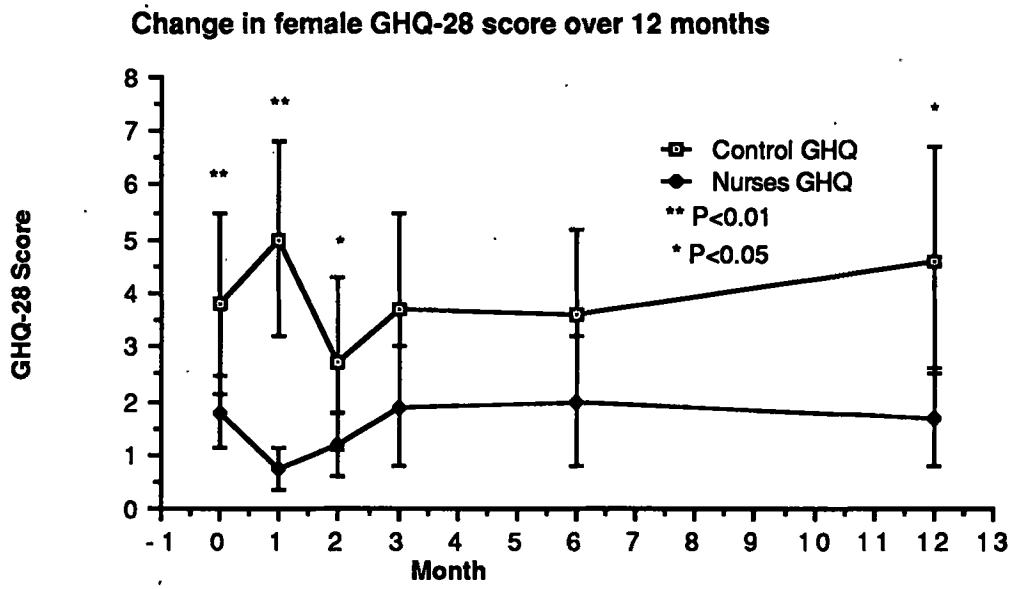
Nurses values: 0 months **n=23;** 1 month **n=12;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.4

The graph below shows the change in female nurses scores on the General Health Questionnaire compared to the female control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.6

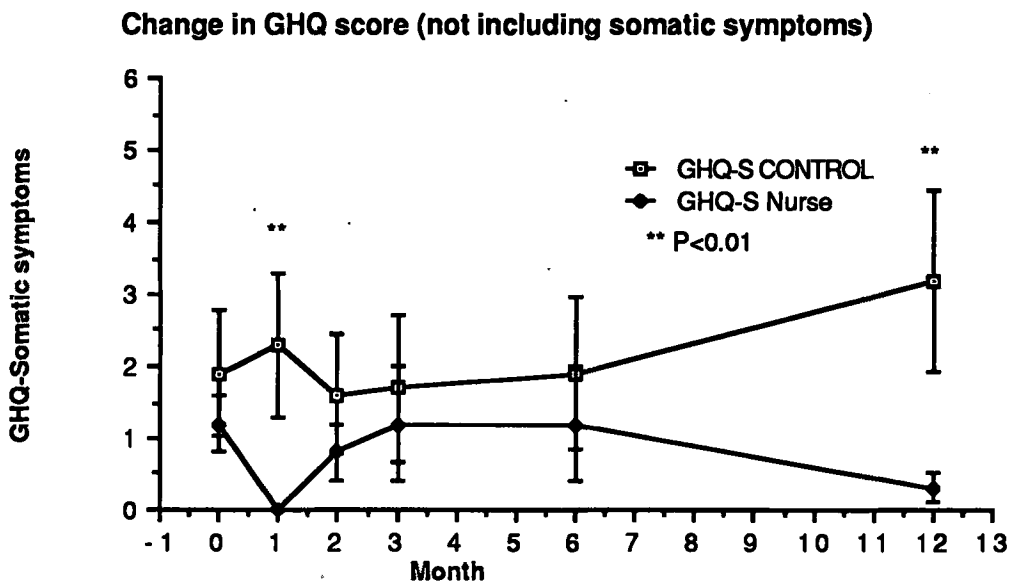
Nurses values: 0 months **n=22;** 1 month **n=12;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.5

The graph below shows the change in nurses scores on the General Health Questionnaire (excluding somatic symptoms) compared to the control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.7

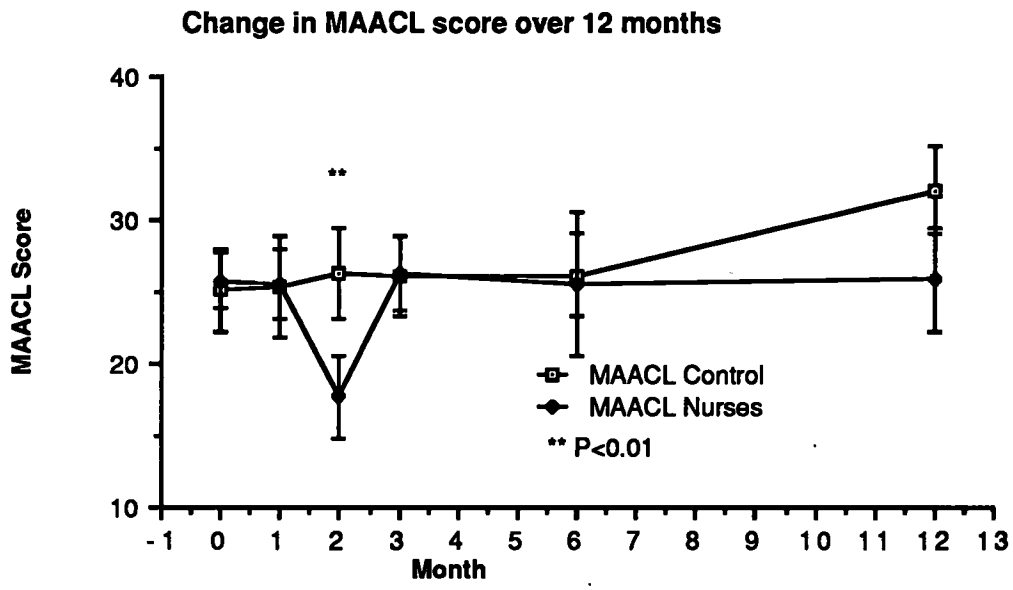
Nurses values: 0 months **n=23;** 1 month **n=13;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.6

The graph below shows the change in nurses scores on the Multiple Affect Adjective Checklist compared to the control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.8

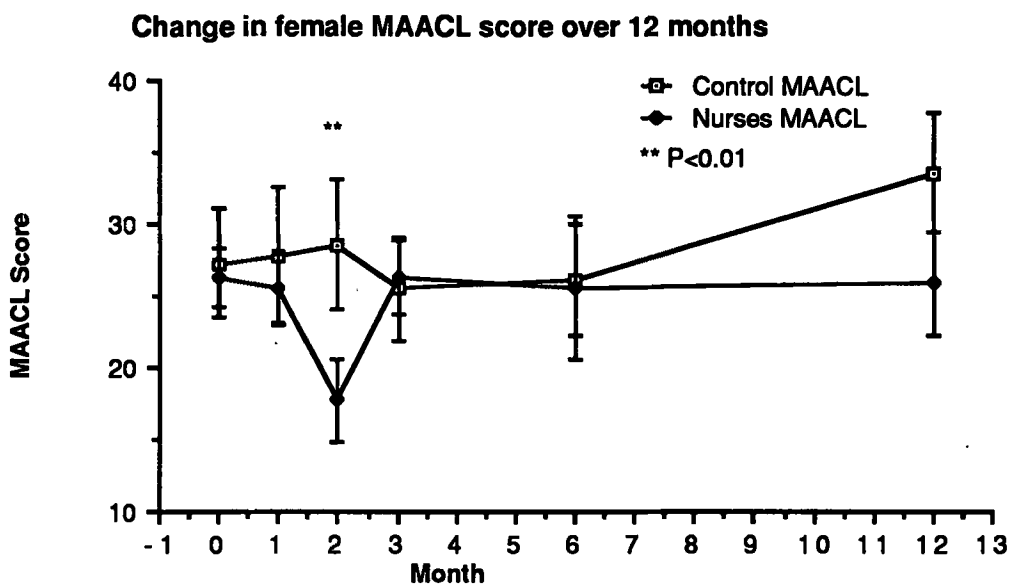
Nurses values: 0 months **n=23;** 1 month **n=11;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.7

The graph below shows the change in female nurses scores on the Multiple Affect Adjective Checklist compared to the female control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.10

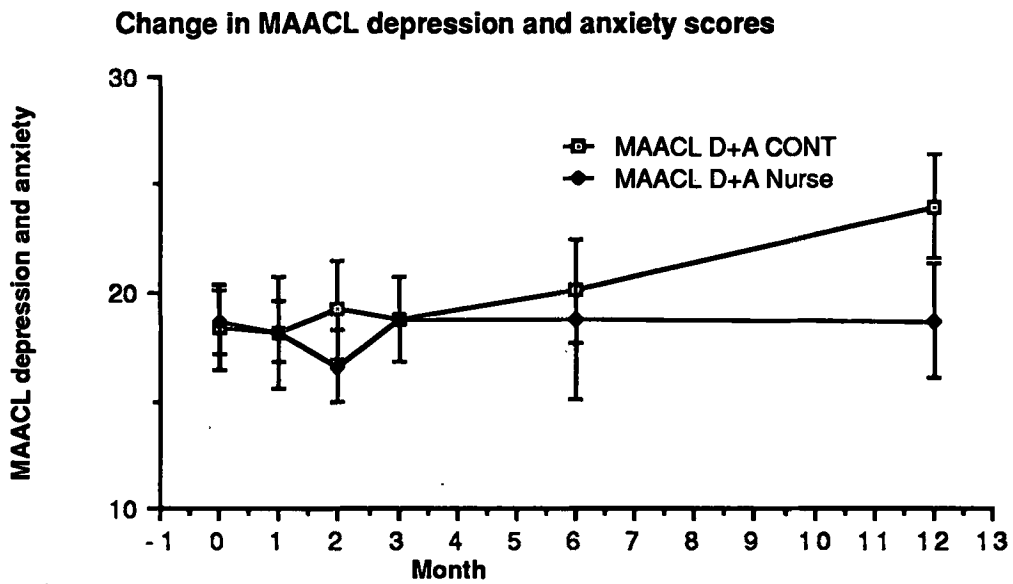
Nurses values: 0 months **n=23;** 1 month **n=11;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.8

The graph below shows the change in nurses scores on the Multiple Affect Adjective Checklist (Depression and Anxiety scores only) compared to the control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.11

Nurses values: 0 months **n=23;** 1 month **n=11;** 2 months **n=17;**

3 months **n=15;** 6 months **n=10;** 12 months **n=7.**

Results are expressed as means +/- standard error of mean.

Discussion of questionnaire results

As with the client and control data a very similar pattern of results has emerged for the BDI and GHQ-28 data, but the MAACL fails to demonstrate any particularly meaningful results. Both the BDI and GHQ scores for the nurses fall below that of the control values indicating that nurses are less stressed than 'normal'. There are three possible reasons for this, the first of which is that nurses really are less stressed than controls. Given the body of literature indicating to the contrary this first explanation is very unlikely. Secondly, because the nurses were studied at work, even though they were assured that their questionnaires would not be passed to their managers, they may have felt some concern that they should come out of the study in a positive light so may have deliberately answered the questionnaires more positively. Thirdly it is possible that the coping mechanisms of nurses are such that they don't allow themselves to believe that they have problems and so on self-report questionnaires of this nature would artificially elevate their scores. The whole issue of successful coping strategies employed by nurses is confounded by methodological differences used in various studies (Bargagliotti and Trygstad 1987) and so is difficult to draw conclusions from.This could perhaps have been solved by the use of questionnaires designed specifically for health professionals or nursing (e.g. the Nursing stress scale Gray-Toft and Anderson (1981))

Changes in the binding assay results over 12 months

[^{3}H] Imipramine binding

The imipramine binding levels seen in the nursing group throughout the study are significantly lower than control levels (0,1,2,3 and 6 months $P<0.01$; 12 months $P<0.05$). These results are highly significant (see figure 9.9) and given the prediction that lowered imipramine binding levels are indicative of depression I would therefore have expected to see increased scores on the psychiatric rating scales indicative of a relatively higher level of psychic distress. However this was completely the opposite to what was observed and may represent a reluctance on the part of nurses to admit to being stressed or possibly very

strong coping mechanisms.

Assessment of change over time by comparing the first and last values using a student t-test, ANOVA and repeated measures ANOVA indicated that there was no significant change in imipramine binding over the duration of the study. As the Nurses group had a higher percentage of females than the control group, it was possible that the different results reflected a gender difference, so the data was also analysed using only the female nurses and female controls (see figure 9.10) A very similar pattern of results emerged with significantly lower imipramine binding values found in the nurses group throughout the study (0,1,2,3 and 6 months $P<0.01$; 12 months $P<0.05$). Male data were not analysed separately due to insufficient data.

[^{3}H] Paroxetine binding

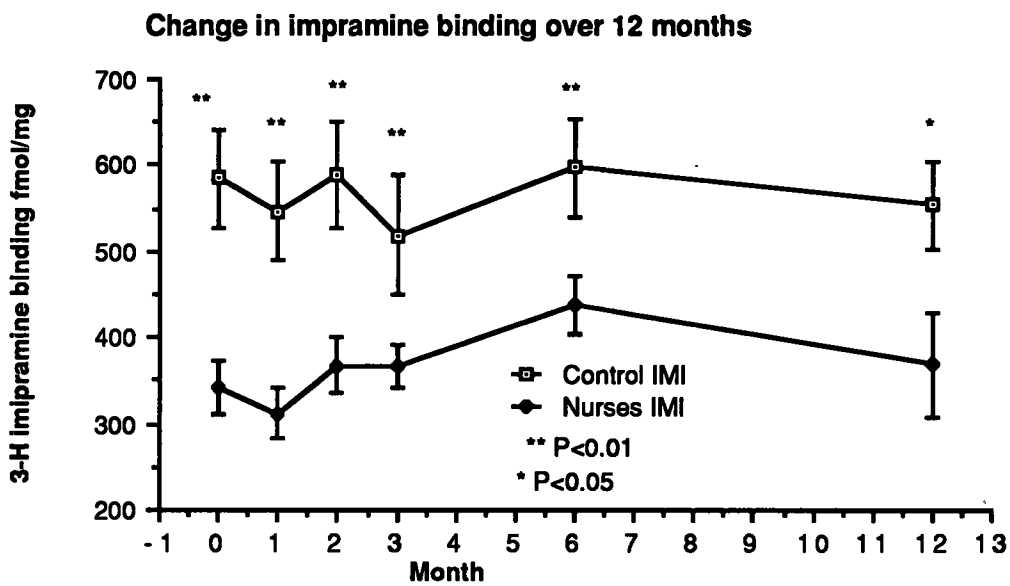
Paroxetine binding was lower for the nursing group than the control group throughout the study (0 month $P<0.05$; 1,2,3 and 6 months $P<0.01$), see figure 9.11 (although no difference was seen between the 2 groups on ANOVA and repeated measures ANOVA assessment). This result is interesting given the fact that no difference was seen between clients and controls and that other research has failed to demonstrate decreased paroxetine binding in depressed patients (e.g.D'haenen *et al* 1988). A number of studies have indicated that paroxetine is a more accurate measure of 5-HT function than imipramine (e.g. Plenge *et al* 1990). Given the much more marked reduction in both imipramine and paroxetine binding seen in the nurses group it is likely that I have actually selected a group with markedly reduced serotonergic function. This may be an age or gender factor but this is highly unlikely given the near equal age distribution and the fact that female imipramine and paroxetine binding values were not significantly different in the client or control groups.

There was no significant change over time for the nurses paroxetine binding results. When only female data was compared the results were very similar, the nurses results being lower than the controls (1 month $P<0.05$; 2,3 and 6 months $P<0.01$). (see figure 9.12). As with

the imipramine binding male data were not analysed separately.

Figure 9.9

The graph below shows the change in nurses ^{3}H-imipramine binding to platelet membranes compared to the control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.13

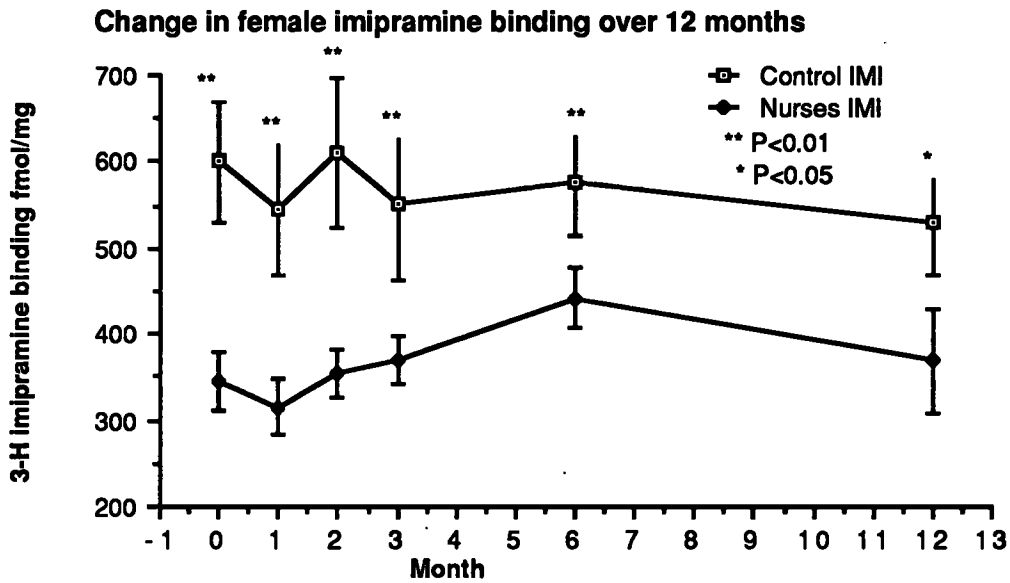
Nurses values: 0 months **n=27;** 1 month **n=14;** 2 months **n=21;**

3 months **n=20;** 6 months **n=16;** 12 months **n=9.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.10

The graph below shows the change in female nurses ^{3}H-imipramine binding to platelet membranes compared to the female control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.15

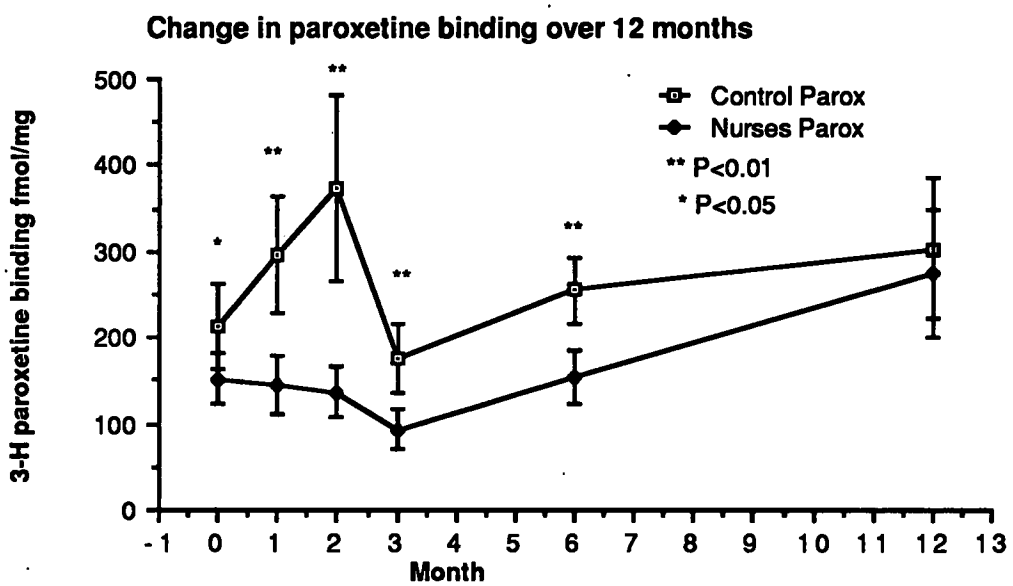
Nurses values: 0 months **n=24;** 1 month **n=13;** 2 months **n=19;**

3 months **n=19;** 6 months **n=15;** 12 months **n=9.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.11

The graph below shows the change in nurses ^{3}H-paroxetine binding to platelet membranes compared to the control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.16

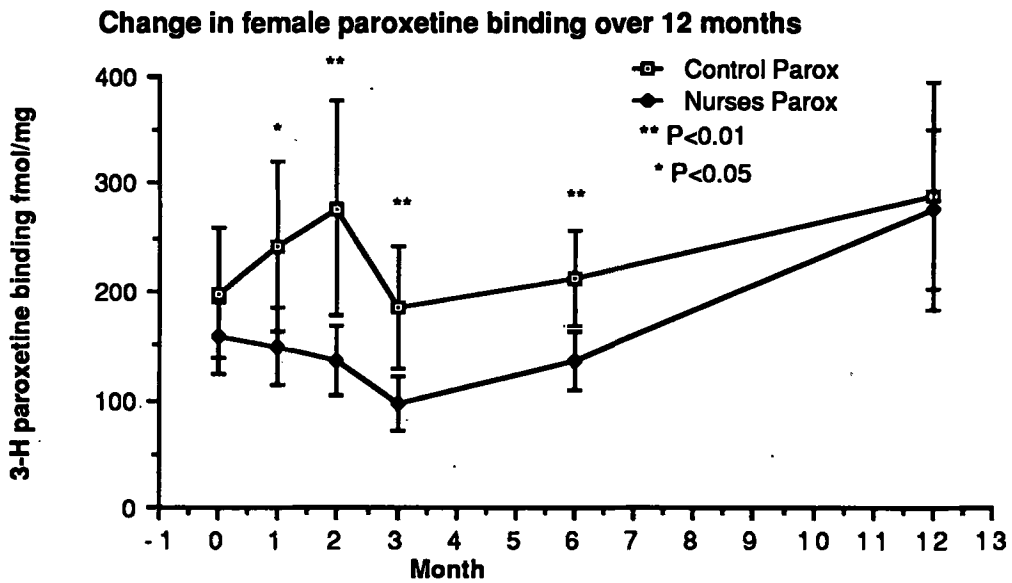
Nurses values: 0 months **n=27;** 1 month **n=14;** 2 months **n=21;**

3 months **n=20;** 6 months **n=16;** 12 months **n=9.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Figure 9.12

The graph below shows the change in female nurses ^{3}H-paroxetine binding to platelet membranes compared to the female control group (population 'normal') over the twelve month period of the study.



Control values: See Figure 8.18

Nurses values: 0 months **n=24;** 1 month **n=13;** 2 months **n=19;**

3 months **n=19;** 6 months **n=15;** 12 months **n=9.**

Results are expressed as means +/- standard error of mean. Statistical analyses shown, were performed using a one tailed students t-test, the control data being taken to represent the population 'normal' value.

Discussion of impramine and paroxetine binding results

These data are difficult to interpret. The first issue that needs establishing is whether or not the nurses were actually stressed/depressed or not. If it is concluded from the imipramine binding results that they were then this study provides evidence of reduced paroxetine binding in depressed subjects. If however if it is believed that the questionnaire data is correct then this study has identified decreased imipramine and paroxetine binding in non-depressed subjects, which to my knowledge has not been observed before. In the previous chapter I briefly alluded to a theory I would like to propose which would account for these results.

In this thesis I have cited numerous examples of research indicative of decreased serotonergic functioning in depression. I have also shown that precise correlations of psychological state to imipramine binding have proved difficult. Whether depression results from serotonergic dysfunction directly or as a consequence of some other factor (physiological or psychological), it would appear that when synaptic 5-HT activity falls below a certain level, depression follows in the patient. Work on women with premenstrual syndrome has indicated that these changes occur ahead of the symptoms of depression (Rojansky *et al* 1991). Therefore it is possible that the nurses coping mechanism maintains them in a state which is more likely to develop into depression than the general population (hence the higher incidence of depressive disorder observed in this group). Some antidepressants act by further reducing the number of 5-HT uptake sites and this may account for the high relapse rate. This would mean that stressed individuals might show decreased imipramine binding without comparable psychological changes.

If this could be proved, it might explain why decreases in paroxetine binding were not seen with the client subjects when they were with the nurses as the clients were already depressed and possibly already beginning to improve at the start of the study.

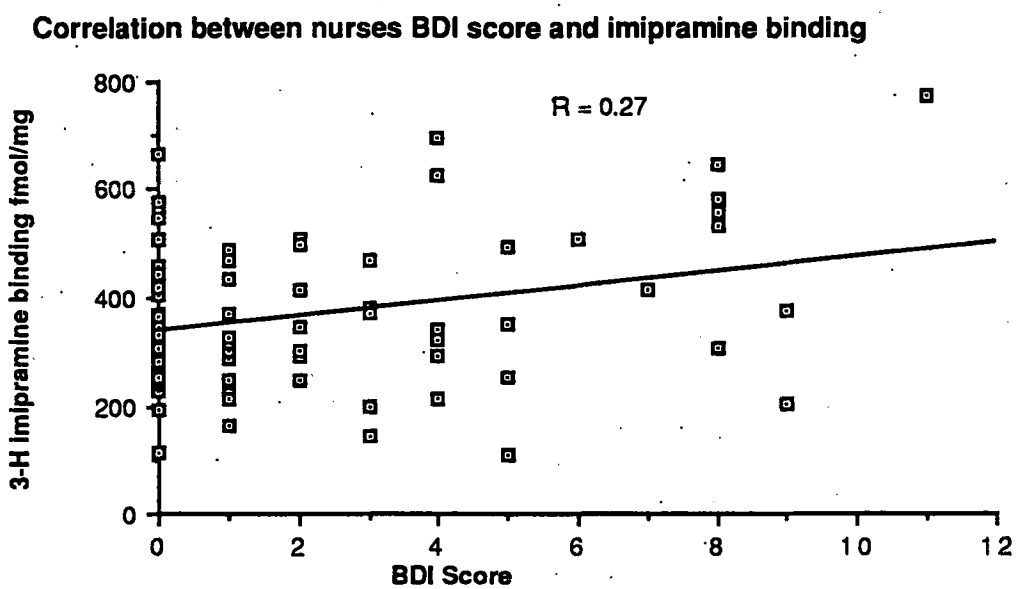
Correlations between binding assays and questionnaires

As already discussed in the previous chapter, it was an aim of this study to demonstrate a correlation between questionnaire scores and platelet binding parameters. However as shown in figures 9.13-9.18, no clear correlation was found between either imipramine or paroxetine binding and any of the questionnaires, although there is possibly a very weak positive correlation between the BDI score and imipramine binding and also GHQ-28 score. However this indicates that as psychological distress increases so does the imipramine binding which is the opposite to what was predicted.

As well as attempting to correlate actual questionnaire values with binding parameters, change since last assessment and change from baseline were also compared and again no significant correlation was found.

Figure 9.13

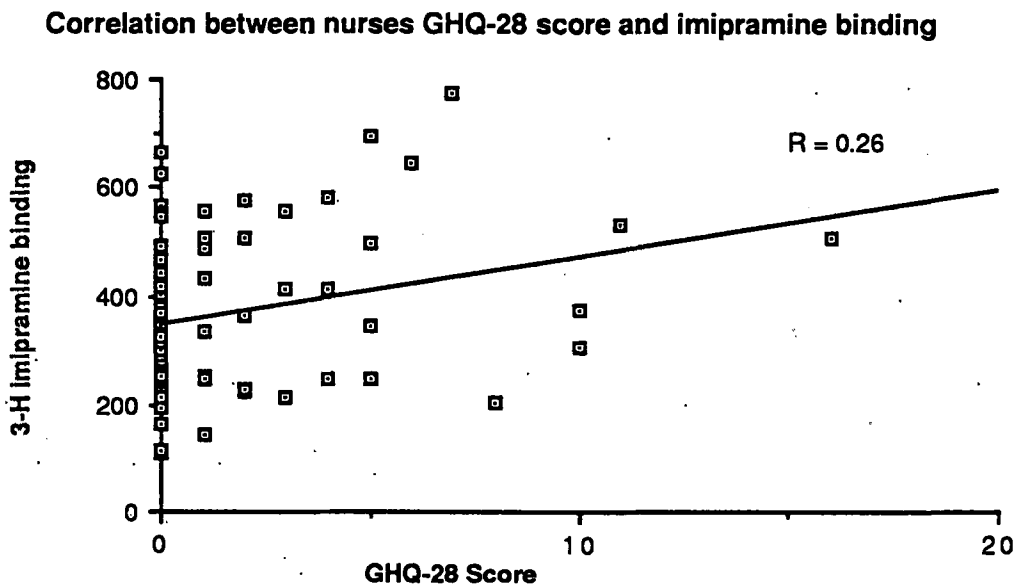
The graph below shows the level of correlation between nurses BDI scores and imipramine binding.



The results shown are from all the nurses data. A very weak positive correlation is apparent.

Figure 9.14

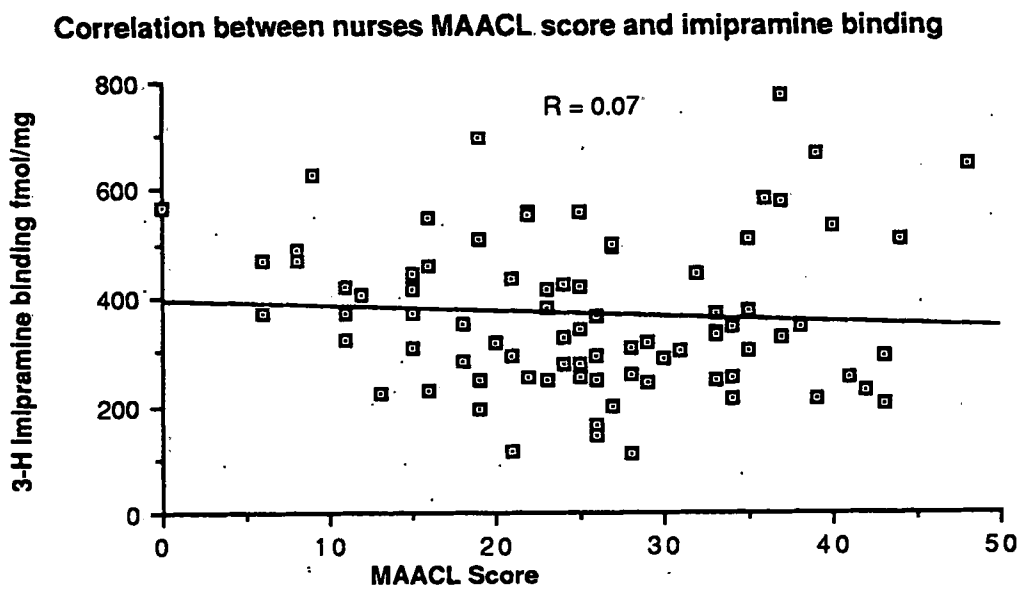
The graph below shows the level of correlation between nurses GHQ-28 scores and imipramine binding.



The results shown are from all the nurses data. A very weak positive correlation is apparent.

Figure 9.15

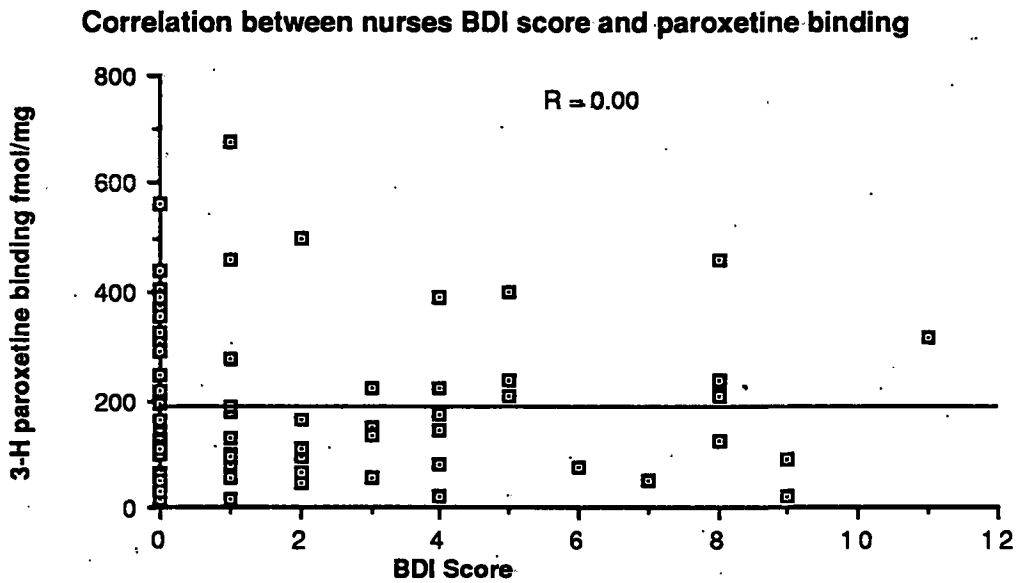
The graph below shows the level of correlation between nurses MAACL scores and imipramine binding.



The results shown are from all the nurses data. No correlation is apparent.

Figure 9.16

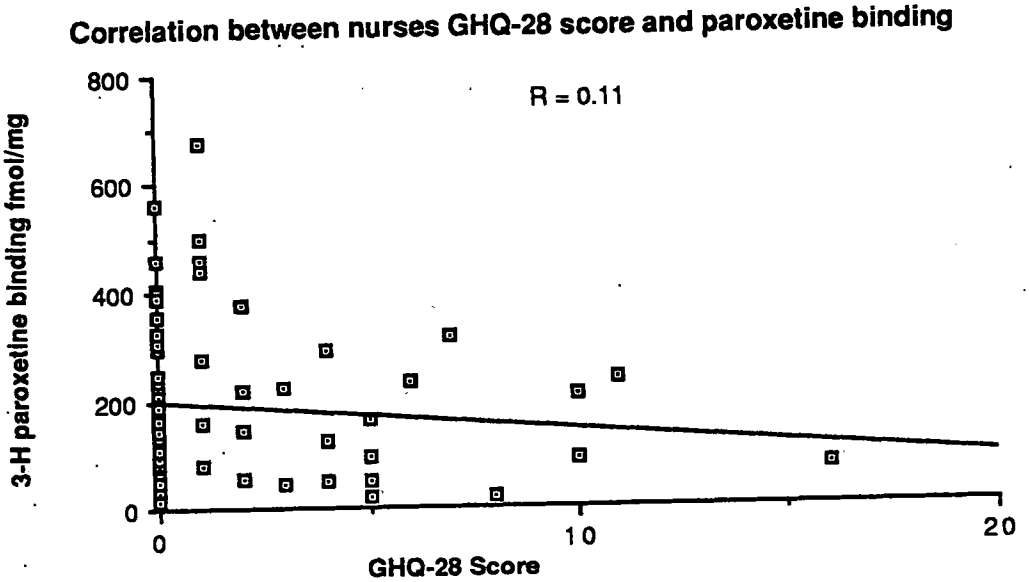
The graph below shows the level of correlation between nurses BDI scores and paroxetine binding.



The results shown are from all the nurses data. No correlation is apparent.

Figure 9.17

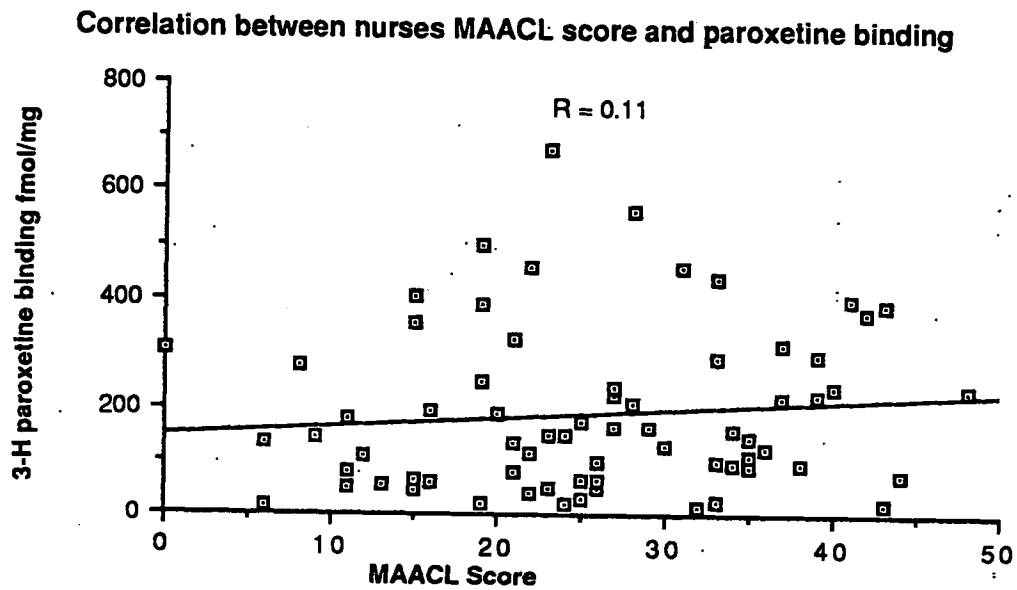
The graph below shows the level of correlation between nurses GHQ-28 scores and paroxetine binding.



The results shown are from all the nurses data. No correlation is apparent.

Figure 9.18

The graph below shows the level of correlation between nurses MAACL scores and paroxetine binding.



The results shown are from all the nurses data, no correlation is apparent.

Discussion of correlation data

There were no clear correlations between binding data and questionnaire data, despite quite marked reductions in both binding parameters compared to the control group. There are a number of different sources of stress and depression amongst nurses which broadly relate to work overload, difficulties in nursing severely ill patients, concerns over treatment of patients and the interdependence on other people (Cavagnaro 1983; Dewe 1987; Lee 1987). However personality and demographic issues also have a very pronounced effect (Ivancevich *et al* 1982; Numeroff and Abrams 1984). Certain areas of nursing obviously have specific stressors associated with their particular area e.g. Operation Theatre nurses (Marcus and Popovic 1985), intensive care nurses (Chiriboga and Bailey 1986; Keane *et al* 1985), terminal care nurses (Gray-Toft and Anderson 1986). Evidence of these stressors may not be easily detected by the GHQ or the BDI as most studies of stress in nursing tend to use specifically developed scales (e.g. Wolfgang 1988). However I had deliberately chosen to use nurses from all wards so as to avoid observing effects that would be limited to one type of nursing only.

If this study was repeated I would recommend the use of the Health Professions Stress Inventory as this would better reflect the stress that is actually perceived by the nurses (Wolfgang 1988).

Seasonality of the data

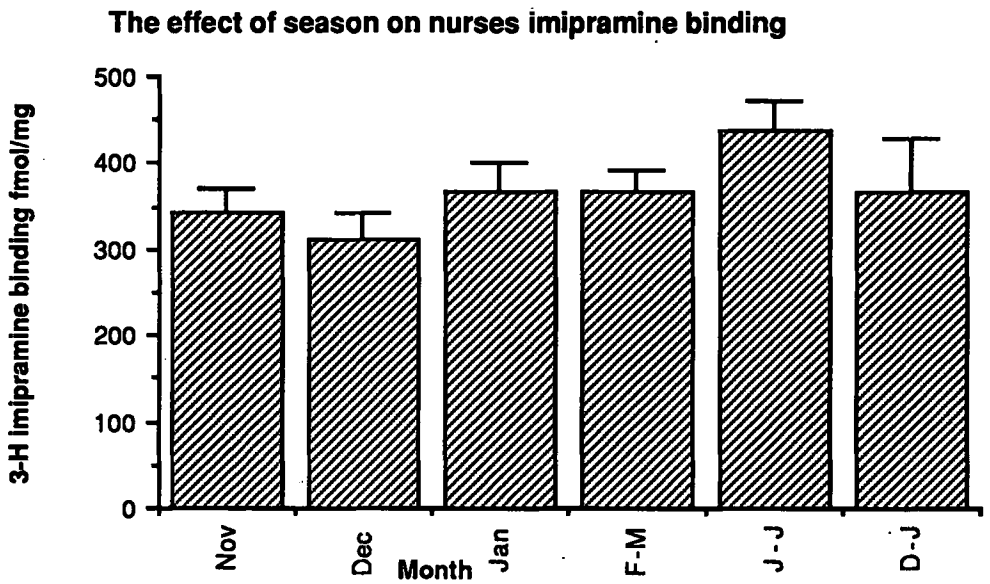
As samples from all nurses were taken at approximately the same time (up to 4 sample days per sample point) the data were already in a seasonal form. However no samples were taken from August to November so the time when lowest values might be expected (around September-November) was not actually available. Highest values for imipramine binding were seen around June/July, to my knowledge this has not been reported elsewhere and only represents a relatively small increase. (see fig 9.19)

High values for paroxetine binding were seen in December-January of the second year but

not December of the first year. This suggests that the changes seen are due to some factor other than seasonality. (see fig 9.20).

Figure 9.19

The graph below shows the effect of seasonality on the nurses imipramine binding

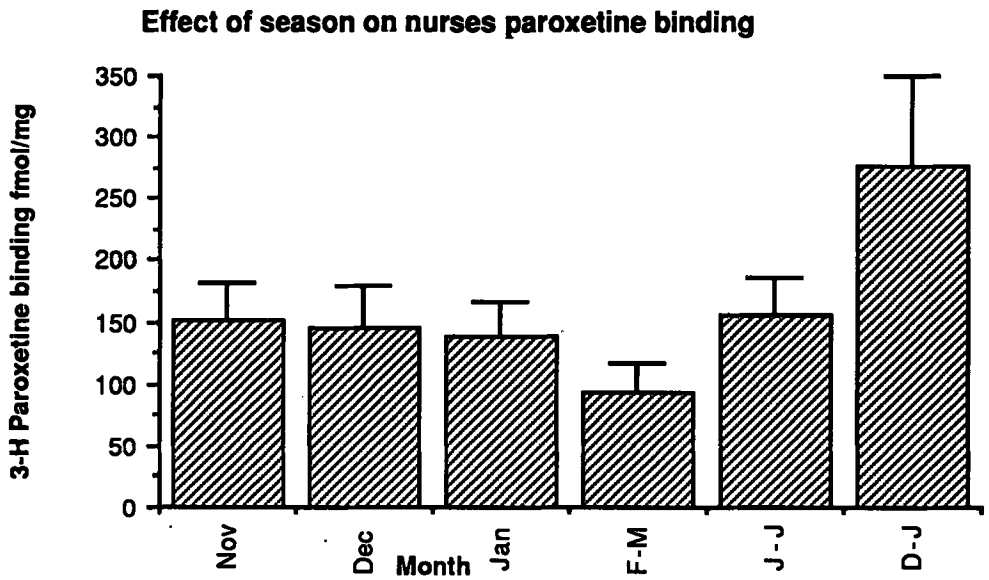


n values; Nov **n=27;** Dec **n=14;** Jan **n=21;** Feb/Mar **n=20;** Apr/May **n=0;** Jun/Jul **n=16;** Aug-Nov **n=0;** Dec/Jan **n=9.**

Results are expressed as means +/- standard error of mean.

Figure 9.20

The graph below shows the effect of seasonality on the nurses paroxetine binding



n values; Nov n=27; Dec n=14; Jan n=21; Feb-Mar n=20; Apr-May n=0; Jun-Jul n=16; Aug-Nov n=0; Dec-Jan n=9.

Results are expressed as means +/- standard error of mean.

Discussion of seasonality data

There was no marked effect of season on impramine or paroxetine binding in these subjects. There was a slight oscillation in the imipramine binding over the year however it was not marked enough to really constitute seasonal changes. The two paroxetine values observed in December were so completely different that a seasonal influence on paroxetine binding would appear very unlikely from these results. However, as with the client and control data, it was not a primary aim of this project to look for seasonal changes and so the project was not designed to pick this up. In addition nurses work shifts, including nights, and this is likely to impact on any seasonal influences.

CONCLUSIONS

The first assumption that nurses would be more stressed than controls was not particularly well supported by these results. The questionnaire values indicated little or no psychiatric disorder in these subjects, however the imipramine and paroxetine binding results were strongly suggestive of depressive disorder.

Perhaps not surprisingly there was no clear correlation between psychiatric rating scales and the binding assays.

CHAPTER 10

GENERAL DISCUSSION AND PROPOSALS FOR FUTURE WORK

In this thesis attention has focussed on the split between psychotherapy and pharmacotherapy. Whilst this split still exists it is encouraging to note that a growing area of overlap for the treatment of depression, particularly in the area of cognitive psychotherapy is developing. There is however a more alarming split evolving concerning the cause of depression. The protagonists in this argument are firstly those that believe that depression (and other psychiatric illnesses) are caused by the genetics of the individual, and secondly those that believe it is entirely environmental. This argument is as fundamental as that between psychotherapy and pharmacotherapy but it is potentially much more dangerous, and is not limited to disorders in mental function, but extends to areas such as intelligence as well (McGue 1989). It is generally accepted that a family history of depression will predispose the individual to depressive episodes themselves (Weissman 1987), but the debate centres around whether mental illness is inherited, environmental or, as some authors have argued a combination of both (Reveley *et al* 1985). This dichotomy shows no signs of resolving in the short term. In a recent article Baron (1991), who favours a genetic cause, argued against equal funding being given to the search for an environmental marker.

The search for a gene for depression has tended to concentrate on family linkage studies using genetic markers (McGuffin 1988 - review). Classical studies using markers such as red cell types and histocompatability antigens have failed to demonstrate any evidence of linkage (Goldin *et al* 1983). However with the arrival of recombinant DNA techniques a whole new spectrum opened up for those in search of a genetic link. In a now famous investigation of the Old Order Amish in the USA, Egeland *et al* (1987) claimed to have found strong evidence for linkage between bipolar depression and the H-ras locus on chromosome 11. However other workers have since excluded any evidence of such a linkage in Icelandic, Irish and North American pedigrees (Hodgkinson *et al* 1987; Detera-Wadleigh *et al* 1987; Gill *et al* 1988; Mitchell *et al* 1991) and it has also proved

impossible to identify any chromosome 11 linkage in unipolar disorder (Neiswanger *et al* 1990; Wesner *et al* 1990) and the claim has been withdrawn as a statistical artifact (Kelsoe 1989). Those most determined to find evidence of genetic linkage have countered these findings with the argument that maybe bipolar disorder exists in more than one form (McGuffin 1988).

Needless to say the X-chromosome has not been left out of this argument, and several studies claim to have evidence of linkage of bipolar disorder to the X-chromosome (Baron *et al* 1987; Mendlewicz *et al* 1987; Mendlewicz 1991).However the data has been reviewed recently and the evidence is far from clear and may represent higher psychiatric morbidity or greater relapse rate rather than a direct link to the disease (Baron *et al* 1990). Interestingly if unipolar disorder is looked at in isolation, evidence of linkage is harder to find (Andreason *et al* 1986; Neiswanger *et al* 1990; Wesner *et al* 1990), in fact McGuffin and Katz (1989) are forced to make the conclusion that neurotic depression is "somewhat less genetically influenced than endogenous depression".

Work has also been conducted on families with high incidence of the more severe mental disorders such as schizophrenia and in this field too there has been limited success (Byerley 1989; Detera-Wadleigh *et al* 1989). Seven pedigrees of families with multiple schizophrenia showed linkage of the illness to a gene on chromosome 5 (Sherrington *et al* 1988), however replication studies found no such linkage, and this claim too, has been withdrawn (Detera-Wadleigh *et al* 1989; Kennedy *et al* 1988). Some authors have argued that there may be a genetic tendency to develop the disease, but that it requires environmental factors for the disease state to become apparent (Goldin *et al* 1987: Freeman 1989). Other authors have argued strongly from a sociological point of view against the dangers of identifying a genetic link for schizophrenia and other disorders (Marshall 1986).

Belmaker (1991) argues five major points against the argument of one gene for each psychiatric illness. Firstly the affective disorders do not fit Mendelian patterns for inheritance. Secondly, identical twins of severe schizophrenic or manic depressive patients may be completely normal. Thirdly, risk figures for offspring of schizophrenic or manic

depressive illness are only 10-20%, ie similar risk to polygenic illnesses such as hypertension. Fourthly, at least 50% of manic depressive or schizophrenic patients have no family history. And finally the boundaries of related disorders are so difficult to define that whatever factors cause the disease must represent a continuum. Thus if genes are involved it is likely to be several genes per psychosis, which is likely to make them very hard to identify. However Crow (1990a) has argued that in psychotic disorders this continuum could relate to changes at a single gene locus, possibly located on the sex chromosomes (Crow 1990b). The search for genetic causes of psychiatric illness continues to push forward and gene loci for major receptors involved in psychiatric disorders are currently being identified (Wahlstrom 1990).

It is reasonably well established that the families of depressed people are most likely to show elements of depressive disorder (Klein 1990). This familial association, however is probably more easily explained from an environmental point of view than by genetics. Alnaes and Torgerson (1990) investigated the amount of parental care given by depressed parents to their offspring. Not surprisingly they found that these parents, particularly those with mixed anxiety-depression had very low levels of parental care, the influence that this is likely to have on child-parent bonding is obviously significant. The effect of early life events on the individuals likelihood of developing depression is high (Garnefski *et al* 1990), and it is well established that certain forms of adversity such as threatening or unpleasant life events may result in the onset of depression (Brown and Harris 1978; Bebbington 1985; Brown *et al* 1987). These events need not be outwardly traumatic, but may be long lasting and the chronic influence may result in depression, e.g. employment status, motherhood (Brown and Bifulco 1990)

Another argument in favour of the environmental standpoint is the influence of external factors in the outcome of the disease e.g. poor family relationships and lack of a confidant, are likely to indicate a poor prognosis (Moos 1990). Coryell *et al* (1990) have demonstrated that single patients who were socially impaired as adolescents are less likely to make a full recovery. If environmental factors have such a major effect on outcome then it is also likely that they have a major influence on onset.

Whilst it is not my intention to argue that there is no genetic involvement in the affective disorders, there may in fact be some genetic predisposition which makes some individuals more prone than others. I would like to argue that environmental factors clearly do exist, and it is these factors which can be most readily studied and acted upon, particularly by psychotherapy. I am not clear of how we will react if and when we find a gene for depression, but the sociological implications are enormous (Marshall 1988). Much of the arguments against psychotherapy have centred around the so called 'non-specific' aspects of treatment, which I would not dispute exist, but also exist in drug therapy. However I would argue that any disease that can be treated by non-specific methods is unlikely to have its origin on a single gene. The relevance of this to the current study really lies in interpretation of results. In the group of nurses we studied we clearly demonstrated according to biological markers that they had lower affect than the controls, and yet according to psychological questionnaires they had higher affect than the controls. The danger of rigid categorisation in biochemical or genetic terms would lead to the conclusion that they were depressed without realising it!. This is obviously incorrect and inappropriate.

I have discussed in earlier chapters the growth in evidence to support psychotherapy as a treatment for depression, and our results seem to support this view. However part of the reason for so determined a search for a biochemical cure (and also to some extent genetic linkage), lies in the ease with which that cure can be administered. The placebo effect in treatment of depressive illness is large and well established (Beckham 1989), and some authors have argued that psychotherapy is no more effective than placebo (e.g. The Lancet 1984). What is clear is that the placebo effect in psychiatric disorders is much greater than in other areas of medicine. Sheperd (1984) argues that ultimately all psychotherapies come down to are responses to demands for reassurance, hope and support. If this is even partly true it would account for the large placebo effect seen in drug studies, but also argues very strongly for more care to be given to patients both in the treatment and prevention of depression.

The costs of providing psychotherapeutic care to patients in addition to drug therapy need not be prohibitive. Group work (such as that used in this study) is very effective as are mutual self help groups (Marmar *et al* 1988) and combination of drug and psychotherapy is generally believed to be efficacious (Blackburn *et al* 1981; Beck *et al* 1985; Weissman 1979; Gastpar 1989). The biggest problem presented by depressive illness is the fact that it is recurrent . Modest benefits have been cited for the long-term use of antidepressants and lithium (Cooper 1989; Persad 1989; Mindham *et al* 1973), but the role of psychotherapy in prevention of further recurrences is likely to be important, and has already been proven, at least to some extent (Shaw 1989; Miller *et al* 1989; Klerman 1989). The results of the psychotherapy part of this research indicated that recurrence rates were low (10.5% compared with reported results of 22% with tianeptine (Raffaitin *et al* 1991) paroxetine 14% (Jakovljevik and Mewett 1991)) and I have suggested that this is indicative of a real recovery rather than a temporary treatment of the symptoms. Frank and Kupfer (1985) have proposed that psychotherapy, either with or without pharmacotherapy presents a very important treatment option for the prevention of relapse. Additionally Aveline (1984) argues very convincingly that the danger of psychiatry without psychotherapy is that the biological label absolves both patient and doctor from the confusion and pain of exploration and comprehension. The danger of this being that only the symptoms will be treated and the underlying cause remain dormant. One factor that I have not discussed, but should be mentioned is the issue of spontaneous remission. Before the arrival of psychotropic medication or psychotherapy, mental hospitals did not overflow. This is because depression is a cyclic illness that will, given time, in the majority of cases, resolve itself and particularly in these mild patients is likely to be a significant factor in recovery.

In an extensive review, Joyce (1989) has investigated the role of non-specific treatment effects on outcome in pharmacotherapy and links them to expectation of outcome both from the doctor and the patient, and the type of patient you are dealing with. Therefore even in pharmacotherapy there is an acknowledged influence of psychological factors. As discussed above there is evidence for longterm efficacy of anti-depressants, and this form of treatment is less demanding in terms of resource, so why not just administer anti-depressants. The answer lies in two main areas, firstly, that it is likely that

anti-depressants are only treating the symptoms rather than the cause, and secondly the potential toxicity of anti-depressant medication. This to some extent is being resolved by the reduced toxicity of modern antidepressants e.g. paroxetine (Dechant and Clissold 1991) but still represents a real problem (Cassidy and Henry 1987; Dziukas and Vohra 1991). However all antidepressant drugs still have side effects even though they are now less severe (Dechant and Clissold 1991). Rouillon (1991) has argued that under some circumstances antidepressants can worsen the course of affective illness while inducing mania or hypomania. Pharmacotherapy is undoubtedly important for the acute treatment of psychological disorders (e.g. Bakish *et al* 1989; Bradwejn 1989) but perhaps the future lies in the coexistence of psychotherapy and psychopharmacology for the treatment of the presenting illness and prevention of recurrence.

What seems fairly clear from this work and previous work discussed earlier is that serotonergic function is in some way altered during unipolar depressive disorder. What still needs to be established is the biochemical link to the depressive symptoms that are evident in these patients. It is well established that antidepressant medication results in down regulation of β-adrenergic receptors, and this down regulation corresponds with the onset of antidepressant efficacy (Banerjee *et al* 1977). More studies clearly need to be performed to evaluate the interaction between the noradrenergic and the serotonergic systems in depression.

Neurochemical theories of depression postulate functional deficits of one or more neurotransmitters at critical synapses in the brain. However attempts to prove decreases in monoamine metabolites in these patients have met with varied success e.g. Asberg *et al* (1984) demonstrated decreased 5-HIAA in CSF whereas Koslow *et al* (1983) found no differences between depressed subjects and controls. Hsiao and coworkers (1987) demonstrated that changes in CSF monoamine metabolites could be shown, but only in those patients who responded clinically to the antidepressants.Sulser (1982) has argued against a monoamine theory of depression on the basis that it cannot explain the delayed therapeutic action of tricyclics, the efficacy of 'atypical' antidepressants, lack of antidepressant action of effective amine inhibitors such as cocaine, variation in clinical

response of agents with similar effects on the amine systems, failure of 5-HTP, tryptophan or L-dopa as antidepressants and finally why some antidepressant treatments decrease amine metabolism. Despite this however the serotonergic theory of depression is probably still the most favoured (Grahame-Smith 1989). A recent electrophysiological study in the rat has demonstrated that tricyclic antidepressants and ECT act by enhancing synaptic transmission by increasing the sensitivity of post synaptic 5-HT_{1A} receptors. On the other hand 5-HT uptake blockers produce their effect by reducing the function of terminal 5-HT autoreceptors thereby increasing the amount of 5-HT released per action potential (Chaput *et al* 1991).

The β-adrenergic theory of depression (ie that depression results from supersensitivity of β-adrenoceptors) has a number of strengths. Firstly, virtually all antidepressant treatments result in down regulation of β-receptors, and secondly that the timescale for this down regulation and antidepressant efficacy are the same. This may also account for the failure in our study to correlate imipramine binding with change in questionnaire scores, we may have been more successful if we looked at β-receptors. The weakness in this theory however lies in the fact that most of the data comes from animals (e.g. Banerjee *et al* 1977; Charney *et al* 1981), human data are few and rely on peripheral studies (e.g. Mann *et al* 1985) and studies on human post-mortem brains of suicides show increased binding (Zarko and Beigen 1983). Also the mechanism by which β-adrenergic receptor desensitisation occurs is poorly understood, although some workers have suggested it may result from a secondary response to enhanced noradrenalin at the synapse induced by antidepressants (Sulser 1979). Another complicating factor is that β-adrenergic down regulation may be a secondary change as a result of desensitisation of alpha 2 receptors, or that the adrenergic receptor cyclase complex itself may be a target for antidepressant action..

The finding that the chronic administration of desipramine reduced the

alpha-2-adrenoceptor inhibition of noradrenalin release in the rat brain (Spyrakic and Fibiger 1980), increased interest in the possible roles of these receptors in depression. Results of platelet binding studies have produced very variable results, however Kafka and Paul (1986) have argued that these findings should be viewed with caution due to the uncertainty of the relationship of the ligand binding to the functional aspects of the adrenoceptor and also that increasing the number of binding sites does not necessarily indicate receptor desensitisation. More recently studies have utilised the the administration of neurotransmitter agonists and antagonists as challenges to study the presynaptic receptor system function in depression (Price *et al* 1986; Henninger *et al* 1988). These studies suggest that patients with major depressive disorder do not have marked abnormalities of alpha-2-adrenergic function.

Overall, however I would tend to support a dysregulation hypothesis (Nair and Sharma 1989) where the homeostatic regulatory mechanism of one or more neurotransmitters becomes impaired. Within this hypothesis it is possible to account for the successful use of a wide range of antidepressants, as well as the varied results seen from binding and similar studies. I think it may be the balance of the neurotransmitters that is important rather than the actual amounts available. A recent report on the anti-depressant efficacy of carbamazapine implicates both noradrenaline and dopamine in its efficacy (Sluzewska 1991), whilst a PET scan study of dopamine and serotonin function in depressed subjects indicated abnormalities for both these compounds in depressives (Agren *et al* 1991) and a significant correlation between peripheral parameters of the two systems has been reported (Castrogiovanni *et al* 1989). It also appears that treatment with antidepressants enhances dopamine function (Maj *et al* 1988; Muscat *et al* 1990). Although the data for the involvement of dopamine are still quite weak the influence of noradrenaline seems quite clear possibly implicating a serotonergic-catecholaminergic regulatory mechanism (Plaznik *et al* 1989). The results we found in this study indicate changes in serotonergic function, but these changes do not correlate with psychometric tests. Perhaps if we had looked at

β-adrenoceptors we might have found a correlation. The future for work in this area must lie in the multiple assessment of neurotransmitter function (as was originally attempted in this study), rather than studies conducted in isolation. By studying covariables we may

identify underlying control mechanisms which would not otherwise become apparent. In the meantime more research is required to investigate the underlying causes of depression from an environmental point of view to enable better cures and better preventative measures.

Future work

The first proposal I would make is that any future work involves the assessment of more than one receptor type. Given the timescale of response of β-adrenoceptor function being approximately the same as the time taken for antidepressant efficacy to be apparent it might be more appropriate for these receptors to be monitored in further studies using lymphocytes (Mann *et al* 1985). Alternatively, there does seem to be reasonably clear evidence of decreased serotonergic function in depressed suicides from measurement of 5-HT_2 receptors (Pandey *et al* 1990), and a method is now available using 3H-Ketanserin to study these receptors in platelets, which has demonstrated a correlation of binding with clinical change (Bigeon *et al* 1990).

Any future proposals for work to continue in this area must attempt as far as possible to reduce confounding variables. Experience gained from working on this project and results obtained from the Primal work, point to areas which could greatly be improved.

For example;

a) To obtain statistical significance a much greater sample size is required, this will necessitate involvement of more centres.

b) Greater selectivity of subjects and controls to ensure subjects are significantly more depressed than controls at the start of the study.

c) More detailed psychological data required (e.g. more extensive questionnaires or researcher administered questionnaires). Also information about recent life-events e.g. giving up smoking, moving house,etc

d) Subjects should, ideally, have a more similar history of therapy. All subjects taken onto the study should be at the start of a period of therapy (or at a fixed time into therapy) and as

far as possible should all be involved in the same amount of therapy, and similar quality therapy.

e) Increased number of samples per subject during the period of therapy. This would make it easier to exclude any widely different values obtained and allow a more clear overall picture to emerge.

A possible direction in which further work in this area could develop would be to seek cooperation from one or more groups of General Practitioners and psychotherapists in the following manner.

Firstly the G.P. would be asked to identify patients within their practise who were currently suffering from depression and receiving drug therapy. If considered appropriate by their G.P. these people would then be approached (by the G.P.) to determine whether they would be prepared to consider psychotherapy instead of drug therapy. If the patient was interested then consent would be obtained and the psychotherapists involved in the work would interview the subject to satisfy themselves of the persons suitability for psychotherapy.

At this point, if appropriate, the person would be accepted on to the study and after a minimum (preferably longer) two week washout period start receiving psychotherapy. Sampling of blood and questionnaires would also begin at this point. All subjects would receive once weekly group therapy for a period of six months, after this time if they wished to continue therapy they would have to make their own arrangements. During the period of therapy all subjects would be sampled every two weeks, then at three monthly intervals after the end of the therapy period for six months.

In summary this enables a group of people who are known to be depressed, to start a period of therapy, with the same therapist, at the same time. The study would allow monitoring of drug-free subjects in therapy for six months, with a six month follow-up period.

If funds permitted, controls could be taken from a volunteer panel to give a more representative control sample than employees at the Open University.

In order to persuade sufficient numbers of people onto the study the cost of their therapy would have to come at least in part from the project budget (unless cognitive therapy was already available at the G.P.'s centre) and this would obviously be expensive. However if all the therapy was carried out in groups, and as much as possible, locally, in order to keep travelling expenses down, then the cost need not be prohibitive.

It should not prove impossible to interest centres involved in cognitive therapy to participate in a study of this nature.

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APPENDIX I

STANDARD CONTACT LETTER

LETTER TO PSYCHOTHERAPY CLIENTS

We are a research group at the Open University in Milton Keynes, interested in discovering how a person's biology might change during a period of psychotherapy. Many theories claim that there is a relationship between a persons body chemistry and their mental state - and indeed the reason why some psychiatrists prescribe drugs to their patients is because the drugs are supposed to change the body chemistry in a way that changes and improves mental state. But up till now no one has tried to find out whether similar changes take place in people going through psychotherapy. If we could show that real changes did occur it would be very exciting scientifically, and it would go part of the way to showing how it is that psychotherapy can help people without using medically prescribed drugs.

The therapists at the Open Centre have very kindly agreed to help us take this research forward by telling their clients about it, and we are now ctively seeking volunteers to participate in the research. If you feel that the project sounds interesting and you would like to become involved, then please fill in the form at the end of this letter. Involvement in the project would require you to complete 3 short questionnaires and have a small sample of blood taken on each of six occasions over the course of a year. Blood withdrawal will be carried out by a properly qualified person using sterile equipment.

We aim to publish the general findings from the study in the scientific literature, but information about any individual will of course be treated in the strictest confidence. Every volunteer entering the study will be coded by number only and their names will not be known or identifiable in any way. However if you would like a copy of your own results and/or the overall findings, these can be made available to you at the end of the study.

If you would like more information about any aspect of the research please do not hesitate to contact me.

Sarah Willis Biology Dept.

I am interested in participating in the study

Name..... Age.....

Please return to:- Sarah Willis
Department of Biology
The Open University
Milton Keynes
MK7 6AA

LETTER TO NURSES

We are a research group at the Open University in Milton Keynes, interested in discovering how a person's biology might change during a period of psychotherapy. Many theories claim that there is a relationship between a persons body chemistry and their mental state - and indeed the reason why some psychiatrists prescribe drugs to their patients is because the drugs are supposed to change the body chemistry in a way that changes and improves mental state. But up till now no one has tried to follow the changes taking place in people whose work makes them more likely to experience anxiety or depression, and who don't receive <u>any</u> form of treatment. If we could show that real changes did occur it would be very exciting scientifically, and it would go part of the way towards demonstrating the problems associated with stressful professions.

The therapists at the Open Centre have very kindly agreed to help us take this research forward by telling their clients about it, and we are now ctively seeking volunteers to participate in the research. If you feel that the project sounds interesting and you would like to become involved, then please fill in the form at the end of this letter. Involvement in the project would require you to complete 3 short questionnaires and have a small sample of blood taken on each of six occasions over the course of a year. Blood withdrawal will be carried out by a properly qualified person using sterile equipment.

We aim to publish the general findings from the study in the scientific literature, but information about any individual will of course be treated in the strictest confidence. Every volunteer entering the study will be coded by number only and their names will not be known or identifiable in any way. However if you would like a copy of your own results and/or the overall findings, these can be made available to you at the end of the study.

If you would like more information about any aspect of the research please do not hesitate to contact me.

Sarah Willis Biology Dept.

I am interested in participating in the study

Name..... Age.....

Tel No..... Ward.....

Please return to:- Sarah Willis
Department of Biology
The Open University
Milton Keynes
MK7 6AA

LETTER TO CONTROLS

We are a research group at the Open University in Milton Keynes, interested in discovering how a person's biology might change during a period of psychotherapy. Many theories claim that there is a relationship between a persons body chemistry and their mental state - and indeed the reason why some psychiatrists prescribe drugs to their patients is because the drugs are supposed to change the body chemistry in a way that changes and improves mental state. But up till now no one has tried to find out whether similar changes take place in people going through psychotherapy. If we could show that real changes did occur it would be very exciting scientifically, and it would go part of the way to showing how it is that psychotherapy can help people without using medically prescribed drugs.

We now require people not currently participating in psychotherapy to act as 'controls'. If you feel that the project sounds interesting and you would like to become involved, then please fill in the form at the end of this letter. Involvement in the project would require you to complete 3 short questionnaires and have a small sample of blood taken on each of six occasions over the course of a year. Blood withdrawal will be carried out by a properly qualified person using sterile equipment.

We aim to publish the general findings from the study in the scientific literature, but information about any individual will of course be treated in the strictest confidence. Every volunteer entering the study will be coded by number only and their names will not be known or identifiable in any way. However if you would like a copy of your own results and/or the overall findings, these can be made available to you at the end of the study.

If you would like more information about any aspect of the research please do not hesitate to contact me.

Sarah Willis Biology Dept.

I am interested in participating in the study

Name..... Age.....

Please return to:- Sarah Willis
Department of Biology
The Open University
Milton Keynes
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APPENDIX II

GENERAL HEALTH QUESTIONNAIRE -28

THE GENERAL HEALTH QUESTIONNAIRE

GHQ 28

David Goldberg

Please read this carefully.

We should like to know if you have had any medical complaints and how your health has been in general, *over the past few weeks*. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

Have you recently

A1 – been feeling perfectly well and in good health?	Better than usual	Same as usual	Worse than usual	Much worse than usual
A2 – been feeling in need of a good tonic?	Not at all	No more than usual	Rather more than usual	Much more than usual
A3 – been feeling run down and out of sorts?	Not at all	No more than usual	Rather more than usual	Much more than usual
A4 – felt that you are ill?	Not at all	No more than usual	Rather more than usual	Much more than usual
A5 – been getting any pains in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A6 – been getting a feeling of tightness or pressure in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A7 – been having hot or cold spells?	Not at all	No more than usual	Rather more than usual	Much more than usual

B1 – lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
B2 – had difficulty in staying asleep once you are off?	Not at all	No more than usual	Rather more than usual	Much more than usual
B3 – felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
B4 – been getting edgy and bad-tempered?	Not at all	No more than usual	Rather more than usual	Much more than usual
B5 – been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
B6 – found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
B7 – been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual

C1 – been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
C2 – been taking longer over the things you do?	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
C3 – felt on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less well
C4 – been satisfied with the way you've carried out your task?	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
C5 – felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
C6 – felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
C7 – been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual

D1 – been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
D2 – felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
D3 – felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual
D4 – thought of the possibility that you might make away with yourself?	Definitely not	I don't think so	Has crossed my mind	Definitely have
D5 – found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual
D6 – found yourself wishing you were dead and away from it all?	Not at all	No more than usual	Rather more than usual	Much more than usual
D7 – found that the idea of taking your own life kept coming into your mind?	Definitely not	I don't think so	Has crossed my mind	Definitely has

A [ ] **B** [ ] **C** [ ] **D** [ ] **TOTAL** [ ]

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APPENDIX III

BECK DEPRESSION INVENTORY

NAME _____(THIS WILL BE REMOVED LATER)

DATE _____

CODE _____(PLEASE LEAVE THIS BLANK)

INSTRUCTIONS:

In each group of statements below, choose the one which best describes how you feel at the moment, and draw a circle round the number at the left of the statement.

A	0	I do not feel sad
	1	I feel blue or sad
	2a	I am blue or sad all the time and I can't snap out of it
	2b	I am so sad or unhappy that it is very painful
	3	I am so sad or unhappy that I can't stand it
B	0	I am not particularly pessimistic or discouraged about the future
	1	I feel discouraged about the future
	2a	I feel I have nothing to look forward to
	2b	I feel that I won't ever get over my troubles
	3	I feel that the future is hopeless and that things cannot improve
C	0	I do not feel like a failure
	1	I feel I have failed more than the average person
	2a	I feel that I have accomplished very little that is worthwhile or that means anything
	2b	As I look back on my life all I can see is a lot of failures
	3	I feel I am a complete failure as a person (parent, husband,wife)
D	0	I am not particularly dissatisfied
	1a	I feel bored most of the time
	1b	I don't enjoy things the way I used to
	2	I don't get satisfaction out of anything any more
	3	I am dissatisfied with everything
E	0	I don't feel particularly guilty
	1	I feel bad or unworthy a good part of the time
	2a	I feel quite guilty
	2b	I feel bad or unworthy practically all the time now
	3	I feel as though I am bad or worthless
F	0	I don't feel I am being punished
	1	I have a feeling that something bad may happen to me
	2	I feel I am being punished or will be punished
	3a	I feel I deserve to be punished
	3b	I want to be punished
G	0	I don't feel disappointed in myself
	1a	I am disappointed in myself
	1b	I don't like myself
	2	I am disgusted with myself
	3	I hate myself

H	0	I don't feel I am any worse than anybody else
	1	I am very critical of myself for my weaknesses or mistakes
	2a	I blame myself for everything that goes wrong
	2b	I feel I have many bad faults
I	0	I don't have any thoughts of harming myself
	1	I have thoughts of harming myself but I would not carry them out
	2a	I feel I would be better off dead
	2b	I have definite plans about committing suicide
	2c	I feel my family would be better off if I were dead
	3	I would kill myself if I could
J	0	I don't cry any more than usual
	1	I cry more than I used to
	2	I cry all the time now, I can't stop it
	3	I used to be able to cry but now I can't cry at all even though I want to
K	0	I am no more irritated now than I ever am
	1	I get annoyed or irritated more eaily than I used to
	2	I feel irritated all the time
	3	I don't get irritated at all at things that used to irritate me
L	0	I have not lost interest in other people
	1	I am less interested in other people now than I used to be
	2	I have lost most of my interest in other people and have little feeling for them
	3	I have lost all my interest in other people and don't care about them at all
M	0	I make decisions about as well as ever
	1	I am less sure of myself now and try to put off making decisions
	2	I can't make decisions any more without help
	3	I can't make decisions at all any more
N	0	I don't feel I look any worse than I used to
	1	I am worried that I am looking old or unattractive
	2	I feel that there are permanent changes in my appearance and they make me look unattractive
	3	I feel that I am ugly or repulsive looking
O	0	I can work about as well as before
	1a	It takes extra effort to get started at doing something
	1b	I don't work as well as I used to
	2	I have to push myself very hard to do anything
	3	I can't do any work at all
P	0	I can sleep as well as usual
	1	I wake up more tired in the morning than I used to
	2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
	3	I wake up early every day and can't get more than 5 hours sleep
Q	0	I don't get any more tired than usual
	1	I get tired more easily than I used to
	2	I get tired from doing nothing
	3	I get too tired to do anything
R	0	My appetite is no worse than usual
	1	My appetite is not as good as it used to be
	2	My appetite is much worse now
	3	I have no appetite at all any more

S	0	I haven't lost much weight, if any, lately
	1	I have lost more than 5 lbs
	2	I have lost more than 10 lbs
	3	I have lost more than 15 lbs
T	0	I am no more concerned about my health than usual
	1	I am concerned about aches and pains, or upset stomach, or constipation or other unpleasant feelings in my body
	2	I am so concerned with how I feel or what I feel that its hard to think of much else
	3	I am completely absorbed in what I feel
U	0	I have not noticed any recent change in my interest in sex
	1	I am less interested in sex than I used to be
	2	I am much less interested in sex now
	3	I have lost interest in sex completely

APPENDIX IV

MULTIPLE AFFECT ADJECTIVE CHECKLIST

MULTIPLE AFFECT ADJECTIVE CHECK LIST

DIRECTIONS: On this sheet you will find words which describe different kinds of moods & feelings. Mark an X in the boxes beside the words which describe how you feel at the present time. Some of the words may sound alike, but we want you to mark all the words that describe your feelings.
Please work rapidly.

1	☐	active	45	☐	fit	89	☐	peaceful
2	☐	adventurous	46	☐	forlorn	90	☐	pleased
3	☐	affectionate	47	☐	frank	91	☐	pleasant
4	☐	afraid	48	☐	free	92	☐	polite
5	☐	agitated	49	☐	friendly	93	☐	powerful
6	☐	agreeable	50	☐	frightened	94	☐	quiet
7	☐	aggressive	51	☐	furious	95	☐	reckless
8	☐	alive	52	☐	gay	96	☐	rejected
9	☐	alone	53	☐	gentle	97	☐	rough
10	☐	amiable	54	☐	glad	98	☐	sad
11	☐	amused	55	☐	gloomy	99	☐	safe
12	☐	angry	56	☐	good	100	☐	satisfied
13	☐	annoyed	57	☐	good-natured	101	☐	secure
14	☐	awful	58	☐	grim	102	☐	shaky
15	☐	bashful	59	☐	happy	103	☐	shy
16	☐	bitter	60	☐	healthy	104	☐	soothed
17	☐	blue	61	☐	hopeless	105	☐	steady
18	☐	bored	62	☐	hostile	106	☐	stubborn
19	☐	calm	63	☐	impatient	107	☐	stormy
20	☐	cautious	64	☐	incensed	108	☐	strong
21	☐	cheerful	65	☐	indignant	109	☐	suffering
22	☐	clean	66	☐	inspired	110	☐	sullen
23	☐	complaining	67	☐	interested	111	☐	sunk
24	☐	contented	68	☐	irritated	112	☐	sympathetic
25	☐	contrary	69	☐	jealous	113	☐	tame
26	☐	cool	70	☐	joyful	114	☐	tender
27	☐	cooperative	71	☐	kindly	115	☐	tense
28	☐	critical	72	☐	lonely	116	☐	terrible
29	☐	cross	73	☐	lost	117	☐	terrified
30	☐	cruel	74	☐	loving	118	☐	thoughtful
31	☐	daring	75	☐	low	119	☐	timid
32	☐	desperate	76	☐	lucky	120	☐	tormented
33	☐	destroyed	77	☐	mad	121	☐	understanding
34	☐	devoted	78	☐	mean	122	☐	unhappy
35	☐	disagreeable	79	☐	meek	123	☐	unsociable
36	☐	discontented	80	☐	merry	124	☐	upset
37	☐	discouraged	81	☐	mild	125	☐	vexed
38	☐	disgusted	82	☐	miserable	126	☐	warm
39	☐	displeased	83	☐	nervous	127	☐	whole
40	☐	energetic	84	☐	obliging	128	☐	wild
41	☐	enraged	85	☐	offended	129	☐	willful
42	☐	enthusiastic	86	☐	outraged	130	☐	wilted
43	☐	fearful	87	☐	panicky	131	☐	worrying
44	☐	fine	88	☐	patient	132	☐	young

APPENDIX V

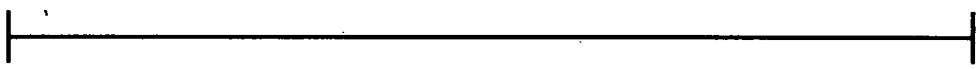
THERAPISTS REPORT

THERAPISTS REPORT

CLIENT:

NUMBER OF WEEKS IN THERAPY: DATE:

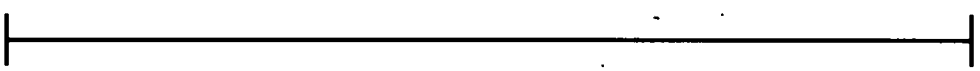
DEPRESSION



not at all depressed — depressed

Please mark the line above according to how depressed the client is, in your opinion at the present time

ANXIETY



not at all anxious — anxious

Please mark the line above according to how anxious the client is, in your opinion at the present time

COMMENTS

If there are any other points you would like to make please list them below